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PATHOLOGY

AND

MORBID ANATOMY.

BY

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CONSULTING PHYSICIAN AND EMERITUS LECTURER ON CLINICAL MEDICINE AT CHARING CROSS HOSPITAL, LONDON, AND CONSULTING PHYSICIAN TO THE BROMPTON HOSPITAL FOR CONSUMPTION AND DISEASES OF THE CHEST.

TENTH AMERICAN

REVISED FROM THE TENTH ENGLISH EDITION.

REVISED AND ENLARGED BY

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PUBLISHERS' NOTE TO THE TENTH EDITION.

A TEXT-BOOK which has reached its tenth edition stands in no need of introduction. Its vigor and vitality bespeak a quality which has won the favor of students and professors alike, namely, a simple, clear and adequate presentation of this groundwork of medicine. Pathology has undergone a transforming growth during the present generation and GREEN has followed in revisions so frequent that its pages might always be consulted for the recent position of its science. This is equally true of the new edition which now carries this sterling work forward.

PREFACE TO THE TENTH ENGLISH EDITION.

THE Ninth Edition of this text-book was thoroughly revised and largely rewritten by Dr. Montague Murray, and the chapter on "Diseases of the Nervous System" was similarly treated by its original author, Dr. F. W. Mott, F.R.S. Hence the work of preparing the present edition has been comparatively light. The text has nevertheless been carefully revised throughout, and considerable additions have been made—additions rendered necessary by the progress achieved in the last few years in certain departments of pathology. These have been most notable in the fields of animal parasitology and of immunity to infectious diseases. I have also had the advantage of studying the syllabus of subjects required by the University of London from candidates in pathology, and have added in accordance therewith a short chapter dealing with "Auto-intoxications and Nutritional Diseases." A few of the older illustrations have been replaced and several new figures added; for these I am indebted, as my predecessors have been, to the skilful draughtsmanship of Mr. T. P. Collings. Messrs. Cassell & Co. have kindly permitted me to reproduce some diagrams illustrating the phenomena of immunity which appeared in my book on "Serums, Vaccines and Toxines" published by them. My thanks are due to Dr. J. M. H. MacLeod and to Dr. Cuthbert Lockyer for the loan of specimens for illustrations; the latter has also been good enough to write for me a short paragraph on "Diseases of the Ovary." My special thanks must be expressed to P. L. Daniel, Pathologist and Curator of the Museum at Charing Cross Hospital, who has most kindly read through the proof-sheets of this volume, and has helped me in innumerable instances with his criticism and advice.

I cannot refrain from expressing the pleasure which it has afforded me to be entrusted by my old clinical teacher, Dr. Green, with the task of preparing a new edition of his well-known Manual. I am, however, only too conscious that the standard set by former editors is so high as to render the attempt to follow them a truly formidable task.

WM. CECIL BOSANQUET.

APRIL, 1905.

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PATHOLOGY AND MORBID ANATOMY.

INTRODUCTION.

PATHOLOGY is the branch of science which deals with the Nature and Causation of Disease. Just as anatomy and histology investigate the naked eye and microscopical structure of the healthy body, while physiology examines the functions of the parts revealed by them, and studies the chemical processes which constitute healthy life, so in the realm of disease we have corresponding divisions—morbid anatomy, morbid histology, and pathology. At post-mortem examinations we note all the naked-eye departures from normal anatomy; with the microscope we discover the finer changes to which these departures are due; and by experimental methods and bedside observations we investigate the causes of the abnormal structure and function, their mode of action, and the nature and sequence of the disturbances which they produce.

All complex organisms can be reduced to very simple elements—the *cells* and the *intercellular substances* to which they give origin. Among the latter we must include the fluids with which the cells are bathed, containing both the nutrient materials for the cells and the excretory products formed by the latter. It is now universally believed that the individual *cell* is the seat of nutrition and function.

In pathology we have to deal not with new tissue-cells and functions, but simply with disturbances of those which normally exist. The cells met with in morbid formations can nearly always be shown to correspond with forms which occur in health at some stage of development; and even the products of morbid degeneration of cells seem, as a rule, to have physiological prototypes. In other words, pathological processes differ only quantitatively from allied physiological processes. New forms of cell-life, both animal and vegetable, are frequently found within the body; but these are parasitic, introduced from without, and are *causes*, not *products*, of disease.

In the study of living things we have to consider two factors—the living organism and its surroundings or environment. The latter includes air to breathe, water to drink, food to assimilate, and warmth, light and other physical conditions necessary to existence. An organism which is suited to its surroundings, and readily reacts to changes in the latter in such a manner as to prolong its own existence, is said to be healthy. By the study of many individuals we arrive at a general

idea of the phenomena which constitute healthy life: this is not an exact standard, but admits of a certain range of variation in the directions both of excess and of defect. Any departure from the normal response to stimulus which goes beyond this range constitutes disease. A *definition of disease* is not easy to construct, but it may for practical purposes be roughly defined as any state of a living organism in which it fails to respond normally to the conditions of its environment; or, in other words, in which there is a failure of some of its normal activities.

The existence of disease is manifested to outside observers by perceptible alterations in the condition of the sufferer, and to the consciousness of the latter himself, in the case of man, by disturbed sensations; these objective and subjective phenomena constitute the signs and symptoms of disease. Disturbances which attract the attention of the sufferer himself are usually termed *symptoms;* those which are discovered by the observation of others are called *signs.* As instances of the former we may mention pain, giddiness, and nausea; of the latter, hardness or swelling of a part and abnormalities in the sounds which are heard on listening over the surface of the chest, or which are elicited by tapping upon it with the fingers. There is no essential difference between the two classes of phenomena; many disturbances are perceptible to both sufferer and observer, such as palpitation of the heart, vomiting, or staggering gait.

Experience has shown that the signs of disease tend to occur in definite groups, or, in other words, that many different individuals suffer from similar combinations of perverted vital activities. These groups of symptoms come to form distinct ideas in the minds of observers, and each group is called *a disease*, and is labelled with a distinctive name. Thus the sudden onset, in a previously healthy person, of pain in the side, shivering, rapid breathing and fever forms a group of phenomena sufficiently characteristic, and recurring with sufficient frequency to attract attention. In course of time this group was recognized as "a disease" distinct from other groups of symptoms, and received the name of *pneumonia.* But further observation showed that, in persons who died after presenting such symptoms, some portion of one or both of the lungs was altered in structure, so as to appear solid instead of spongy; and this underlying physical condition came to form part of the idea of the disease: indeed, in conditions in which well-marked structural alterations are found to exist, these form a more important part of the connotation of the name applied to the condition than do the external manifestations, which are liable to vary considerably in individual instances.

As knowledge advanced still further, constant precedent conditions or *causes* became recognized as associated with certain diseases: thus it was noted that exposure to cold often preceded an attack of pneumonia, while in recent years it has been discovered that many diseases are the effects produced upon the body by the invasion of minute vegetable or animal organisms, which grow in the fluids of the living

tissues and produce poisons capable of injuring the component cells. Different parasitic organisms are found to be responsible for different diseases. The question then arises, whether we are to include in the definition of a disease the cause which produces it—whether, for instance, the term "diphtheria" should be limited to cases of sore throat in which a certain bacillus is found, or should continue to be applied to all cases of sore throat in which there is formation of a false membrane in the fauces. The tendency at the present day is in the direction of defining diseases according to their causes rather than according to their clinical features; but it is well to recognize that by so doing we are altering the connotation of well-established medical terms.

Varieties of Disease.—Distinguishing, as we have done, the living organism from its surroundings or environment, we see at once that causes of disease may be roughly classified into (*a*) those arising out of defects in the original constitution of the individual, or **hereditary** disease; and (*b*) those produced by abnormal or hurtful external circumstances, or **acquired** disease. Thus, on the one hand, a person may be born with gross or minute structural defects, rendering some organ incapable of performing its normal function; or certain of his tissues may be defective in that they rapidly degenerate or wear out. On the other hand, injury may be inflicted by external agents—by cold, heat, or mechanical violence, by poisons taken in with the food, or by the entrance of parasitic organisms. When, however, we look a little more closely into the matter, we find that no definite line can be drawn between these two classes of diseases. Thus a parasitic organism may be unable to establish itself in the body and induce disease except in the presence of some hereditary defect in resisting-power on the part of the individual; while those who are the subjects of manifest hereditary weakness may be able to survive if their surroundings are modified—as premature babies may be reared in artificial incubators, or "bleeders" may suffer no inconvenience if protected from all possible sources of mechanical injury—the congenital defect consisting in a failure of these organisms to adjust themselves to ordinary external conditions, which in these cases are actually injurious.

The two classes of diseases thus distinguished must be considered in rather more detail.

Inherited Disease.—The tendency to *inherited* disease either exists in the ovum at the commencement of development, or is acquired by the ovum in fertilization; tendencies formed later are obviously *acquired*. As in normal development certain organs manifest their inherited tendencies many years after birth—*e. g.*, the development of the female generative system at puberty and its atrophy at the menopause; so inherited tendencies to disease may not show themselves until late in life, as is the case in cancer of the breast or of the uterus. It is possible that in many cases the same unrecognized conditions which induced in a parent the morbid tendency handed down, continue to act on the offspring until—with or without some obvious exciting cause—the disease becomes evident. We cannot say when this tendency to disease

begins: it may have been slowly gaining strength for generations. The fact that no progenitor had the disease in question, if he or she lived well past the age at which such disease usually manifests itself, shows simply that the causes had not acted long enough or with sufficient energy to produce it. It is important to recognize that even inherited disease has its starting-point in conditions external to the cells of the body. We must also bear in mind that every individual is the offspring of two parents, from both of whom characters are inherited. Those of one parent may either be neutralized by opposing characters in the other parent, or may be reinforced if identical tendencies exist on both sides.

With regard to the actual mode in which disease is inherited, it is in some cases probable that the poison, the actual cause of the disease, is present in the ovum or spermatozoon, as has been shown to be the case in the silkworm disease (Pasteur). But how disease and tendencies to diseases which are not due to any specific poison are handed down, we know no more than how it is that children inherit the features of their parents.

Often, no actual disease is inherited, but the power of resistance of certain tissues against the causes of certain diseases (*e. g.*, tubercle) is more or less impaired; or the tissues degenerate early, especially in the fatty or calcareous manner, so that many members of a family may die at about the same age from fatty heart or from a ruptured artery (*apoplexy*).

Acquired Disease.—Diseases occurring in an organism or part possessed of normal vital energy must necessarily be the result of external conditions. The chief causes of acquired disease are: mechanical injuries, extremes of heat and cold, alterations in the pressure of the atmosphere, electrical shocks, defective food, lack of air and sunlight, mineral and vegetable poisons, and parasitic organisms. In pathology the distinction popularly drawn between "injury" and "disease" cannot be maintained.

Disease may be acquired during intra-uterine life—*e. g.*, variola, syphilis, tuberculosis.

General and Local Disease.—Any change in external conditions acting upon a unicellular organism would probably affect every particle of its substance and modify all its functions; all its diseases would therefore be *general*. But multiplication of cells and specialization of functions enable abnormal conditions to act upon certain groups of cells and to disturb their functions without affecting—primarily, at least—those of other groups. We thus get *local* disease; and the great majority of diseases belong to this class.

The complete healthy life of a cell consists in the perfect performance of all its functions. For this it is necessary not only that its structure and vital energy should be normal, but that the nutriment which it receives should be sufficient and suitable, and that its surrounding conditions—pressure, temperature, and connections with other tissues—should be normal. Failure in any one of these will lead to defective action or death of the cell—often spoken of as "disease" of the cell—with resulting disease of the organism as a whole.

Disease affecting *primarily* one part only may be followed by *secondary* affections of other organs: indeed, it is probably impossible for any "local" disease to exist without disturbance of the general economy, though this may be so slight as to escape the notice of observers. As an instance of a primary local disease followed by secondary general disturbance, we may quote Addison's disease or tuberculosis of the suprarenal bodies; destruction of these glands is followed by pigmentation of the skin and vascular disturbance, with rapidly fatal result. Many diseases, apparently primary, are in reality secondary to other lesions due to ill-recognized causes. Thus myxœdema, the condition arising from defect of thyroid secretion, is in reality a secondary condition, the primary disease being atrophy of the thyroid gland, arising from unknown causes; and paralysis caused by embolism of a cerebral artery is secondary to some affection of the heart.

Structural (Organic) and Functional Disease.—A disease is referred to an organ or tissue during life by its symptoms and by its physical signs; and, after death, the localization is justified by the discovery in that part of the same structural change in every case. This is *structural*, or *organic*, disease. Diseases in which no visible or chemical change has been found are sometimes classed as *functional;* the belief being that in them the functions of certain cells are abnormally performed, without any structural change. Very brief reflection shows that this conception involves an impossibility, since the function of an organ or cell is merely alteration of its structure—gross or minute—in response to stimulus: consequently the same structure must, under identical conditions, always perform the same function. "Functional disease" is therefore a term which merely denotes morbid conditions of which the underlying structural (molecular) changes have not been discovered.

Etiology of Disease.—The causes of disease are often divided into two classes—*Predisposing* and *Exciting.*

In so far as this division represents any useful distinction, and is not a mere survival of scholastic logical subtleties, it serves to separate causes of disease into: (1) conditions which act upon the living organism so as to render it susceptible to outside agents, and (2) those agents themselves. Thus starvation or overwork may render a person susceptible to attack by a parasitic organism which would otherwise be unable to settle in his tissues and cause disease. In discussing the subject of immunity we shall have occasion to consider the mode of action of such predisposing causes. It is only in reference to diseases produced by the action of parasites that the distinction of "predisposing" and "exciting" causes appears to have much meaning. The term **predisposing** is, however, applied to certain natural conditions of the body which influence the occurrence of morbid processes. Chief among these are Age, Sex, and Heredity.

Age.—The special liabilities of *childhood* are to some extent explained by supposing that the power of resisting injury, which all cells possess, is not fully developed until adult age; further growing tissues are liable to certain affections which do not occur in adult cells—*e. g.,*

rickets. In *old* age the vital powers are wearing out and degeneration is occurring.

Sex.—The organs peculiar to the sexes render each liable to special diseases. Women are also the special victims of hysteria and chlorosis. We cannot explain the greater liability of women to endemic and exophthalmic goitre and to myxœdema, nor their comparative immunity from Addison's disease, locomotor ataxia, and progressive muscular atrophy.

Heredity.—It has already been stated that feeble vital power, without actual disease, may be the heritage of the body, or of one of its parts. It may further be noted that, like physiological and personal peculiarities, disease—*e. g.*, gout—sometimes skips one or more generations (*atavism*). In other cases, as in hæmophilia and pseudo-hypertrophic muscular paralysis, the disease appears generally in the males only; although the females may, without themselves manifesting it, transmit it to their offspring.

Among the diseases which most obviously "run in families" are: functional nervous disorders, such as hysteria, neuralgia, epilepsy, and insanity, which are more or less interchangeable; carcinoma, especially of the breast and uterus; some simple growths, especially if multiple (lipomata, osteomata, papillomata); gout and tubercular disease; retinitis pigmentosa and color-blindness.

Exciting Causes.—We have already enumerated the principal external causes of disease (p. 20). Certain secondary causes acting locally upon the cells must, however, be mentioned.

Abnormal Blood-supply.—Defects in the blood-supply may be due to errors in the circulation or in the composition of the blood. A defective blood-supply may result from hyperæmia or anæmia; and from all abnormalities in the constitution of the blood, due either to faults in its formation or purification, or to the presence of poisons, whether formed by the cells of the body or by parasitic organisms, or introduced from without.

Abnormal Local Conditions.—In this group we may include the results of mechanical obstacles to discharge of function—*e. g.*, stricture of a duct or orifice, strangulation of gut, pressure arising from neighboring structures, and the mechanical effects of parasites.

Altered Nervous Influence.—The nervous system apparently exerts a direct controlling influence over some, if not all, of the other tissues, and perversion or impairment of this influence causes disturbance of nutrition in the cells affected. Thus in cases of injury to spinal motor nerves the muscles supplied by them rapidly degenerate, and in certain cases of affection of the posterior spinal root-ganglia, inflammation takes place in the corresponding area of the skin (herpes zoster). In locomotor ataxia and syringomyelia acute inflammation and disorganization of some of the joints may occur; and perforating ulcers of the foot appear to be associated with similar defects of nerve-supply. Total loss of hair has occurred as a result of shock, which may also determine the onset of such affections as diabetes or exophthalmic

goitre. The extent of the "trophic" influence of the nervous system is not yet determined.

Effects of Previous Disease.—Some diseases, when they have occurred once, tend to recur again and again. In the case of others, to have suffered once is to have secured practical immunity against a second attack. (See Immunity.)

Certain other diseases, again, seem to modify very deeply the functions of the body. Many years after these diseases, it is found that illnesses, which seem at first sight to have nothing to do with them, yield only to the treatment proper for the original malady. Such are malarial fever, syphilis, and gout. The causal agents of the first two are probably still latent in the body: as to gout, though its pathology is not yet fully made out, it is possible that all its manifestations are due to the deposition of biurate of sodium in the tissues concerned.

Modes of Extension of Disease.—Extension of disease may be effected by spread of the causal agent to neighboring parts; or secondary lesions, as already mentioned, may be caused by failure of function in the part first affected. Extension thus takes place:

1. *By the carriage of the causes of disease from a primary focus to neighboring or distant parts.*—Thus organisms may be carried by the *lymphatics*, and give rise to inflamed lymphatic glands, and cells of malignant tumors are detached and deposited either in neighboring glands or in distant organs, in which positions they give rise to other tumors; pieces of clot may be conveyed by the *bloodvessels* and produce embolism; and a renal calculus may be transferred through the ureter to the bladder. The so-called "direct extension" of inflammation is due to carriage of infective organisms and their toxins by the lymph-stream to the tissues in continuity with the primary focus.

2. *Mechanically*, by so-called "*back-telling.*" Thus stricture of the urethra causes hypertrophy of the bladder, if the obstacle to the outflow of urine can thus be overcome; or simple dilatation of the bladder, if its efforts are futile. In either case the difficulty of entry of urine into the bladder is increased, and the ureters, pelves, and kidneys dilate. Interstitial nephritis results from the pressure, the renal functions are imperfectly performed, and this is detrimental to the organism at large. The succession of changes which result from incompetence of the mitral valves is another familiar example of this mode of extension of disease. (See Passive Hyperæmia.)

3. *Failure of any part to do its share of work in the economy.* The result of such failure will depend upon the readiness and completeness with which its defects can be compensated. If the work can be readily taken over by other parts, as can that of a sweat- or sebaceous gland, nothing is noticed; on the other hand, extirpation of a kidney which was doing work is followed by a time of danger from the consequent interference with the excretion of waste products, and with the formation of the internal secretion of the organ, as the other kidney is at

first unequal to the double duty. Absolute failure of the cardiac or of the respiratory function will cause death, there being no power of compensation.

Terminations of Disease.—The possible terminations of disease are *recovery*, or return of the part to the discharge of its normal functions; *partial recovery;* and *death*, or complete cessation of function. Certain diseases can scarcely be said to have a termination; when once established they remain stationary.

Tissues which are the seat of disease have a natural tendency to recover—*i. e.*, to return to their normal condition, when the morbid process has not been sufficient to cause grave structural damage. An experiment of Lister's illustrates this tendency: If a hot iron be brought near to normally acting ciliated cells, detached from the body, the first effect will be to increase or stimulate the movement of the cilia; but if the hot iron be kept near them long, or brought closer, the movement becomes slower and finally ceases. If the iron be then removed, the cilia will, after a period of quiescence, begin to work again. We may compare this property of living tissue with the behavior of a body placed in stable equilibrium, which tends to return to its original position, if displaced.

The power of resisting injurious agencies varies not only in different individuals, but in different tissues. Not only does a "strong" man recover from a disease which would be fatal to a weaker one, but we find experimentally that a rabbit's ear will resist the effects of anæmia longer than will a knuckle of its intestine or the cells of its central nervous system. In the case of the intestine, the presence of micro-organisms capable of invading the damaged tissues must be borne in mind.

It will be useful here to give a list of the morbid process to which all organs are more or less liable:

Developmental errors.

. . .

Results of mechanical injury.
Displacement.
Hemorrhage.

. . .

Anæmia.
Hyperæmia.
Œdema.
Atrophy.
Degeneration.
Necrosis.

Inflammation (reaction to irritants).
Regeneration.
Hypertrophy.

Tumor-formation.

. . .

Lodgement of parasites.

. . .

Stricture and its consequences may occur in any duct or canal; and calculi may develop in any of them.

Regeneration is included in the above list, since, although it is not itself a morbid process, it is the result of injury or disease, and is therefore intimately connected with pathology; while the products of the reparative process often differ from the original tissue of the injured part.

CHAPTER I.

MALFORMATIONS.

THE term **malformation** is applied to structural defects of parts and organs, the result of errors or accidents in the process of development.

It is customary to classify malformations into three groups: (1) malformations by excess, (2) malformations by defect, and (3) malformations by perversion.

(1) *Malformations by excess* include all double monsters; all repetition of parts or of structures—*e. g.*, supernumerary fingers and toes; and all giant-growths, whether general or local.

(2) *Malformations by defect* comprise all those due to arrest of development. The large majority of these arise at an early period of embryonic life. In this group are included dwarfing and the absence or defective formation of parts, provided they are due exclusively to the *arrest* of normal processes, as in harelip, cleft palate, cleft sternum, and imperforate anus.

(3) *Malformations by perversion* include those congenital errors in which the process of development is irregular and disorderly. In this group are placed, among others, the transposition of viscera and many forms of congenital heart disease.

This classification is, however, not so useful as one based upon the normal order of events which occur in the course of development.

In the space available for this subject it is not proposed to deal with the formation of *double monsters*, whether derived from two ova or from a single ovum, nor with such grave disturbances of development as may lead to any of those abortive results of impregnation which are grouped together under the term *mole*. *Dermoid cysts* are considered along with other cysts at the end of the chapter on Tumors.

A very considerable number of the malformations commonly met with depend on imperfect union in the posterior or anterior median line of the body.

Defective Development in the Posterior Median Line.—It will be remembered that the whole of the central nervous system is developed from an invaginated fold of epiblast known as the neural or medullary groove, which subsequently becomes converted into a canal and separated from the originally adjacent epiblast by a thin layer of mesoblast.

The grossest forms of malformation depend upon the failure of the neural groove to form the neural canal. Thus, both cranium and brain may be absent (*anencephalus*), and the spinal canal and spinal cord may remain an open groove (*open spina bifida*). These conditions, as well as many other malformations of the brain, are incompatible with life, and are, therefore, of little practical interest.

A lesser degree of spina bifida often occurs, in which a hernial pro-

trusion either from the central canal of the spinal cord or merely from the spinal canal, combined with defective formation of the arches of the vertebræ, forms a central tumor in the back, usually in the lumbar region.

When the tumor consists of a protrusion from the *central canal of the spinal cord*, its wall is lined internally by nerve-roots and rudiments of the spinal cord (*syringomyelocele*). When the protrusion arises only from the *spinal canal*, and not from the centre of the spinal cord, the latter generally runs across the cavity and is attached to the middle of the projecting wall of the protrusion, giving rise to a central depression in the tumor when viewed from behind: thence it turns back, and, as the *filum terminale*, reaches the canal again. In such cases (*myelomeningocele*), as well as in those which contain only fluid (*meningocele*), the wall of the tumor is formed of the ordinary integuments lined by the rudimentary spinal meninges. Similar pouches may be formed in connection with defects in the cranium. They generally arise from the occipital region. They may contain brain-substance (*encephalocele*), or brain-substance and fluid (*encephalomeningocele*), or fluid only (*meningocele*).

Malformations of both brain and spinal cord may also arise after the cranium and vertebral column are formed. These comprise (1) a uniform smallness of the brain (*micrencephalia*) or of the spinal cord (*micromyelia*) in which the former may be from two-thirds to one-sixth its natural size; (2) irregular defects in the cortex of the brain in which some of the convolutions are absent, and others small and thin; and (3) more or less extensive depressions or clefts in the cortex due to defective development and constituting the condition known as *porencephalia*. The cerebrum and cerebellum are more liable to malformations than the central parts of the brain. The spaces resulting from the defects in the cortical or central parts, occurring after the formation of the cranium, are filled up by cerebrospinal fluid—in the ventricles or in the subarachnoid spaces, as the case may be. When the defects are marked and the quantity of fluid is large, the condition is known as *congenital hydrocephalus*—*internal*, if the fluid is in the ventricles, and *external*, if it is on the surface of the brain.

The majority of instances of malformation are probably due to primary developmental errors. Injury and circulatory disturbances may be the initial causes in the rest.

Defective Development in the Anterior Median Line.—Defective development and coalescence of the structures forming the anterior median line include a large number of common malformations. The imperfect union is generally attributed to some primary germinal defect or regarded as the indirect result of amniotic bands and adhesions.

If the growth of the nasofrontal and both superior maxillary plates (Fig. 1) be defective, a large gap, involving upper lip, nose, and palate, will be left.

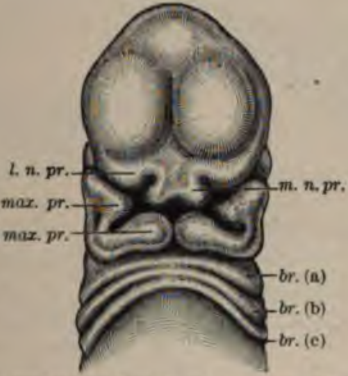
If the defect be confined to the failure of coalescence on the part of the nasofrontal and one maxillary plate, a cleft in the upper lip (*harelip*) will be produced on the corresponding side of the mid-line. If the coalescence of the maxillary plates and corresponding soft parts to form

the palate be incomplete, a central cleft (*cleft palate*) will occur in the posterior part of the roof of the mouth. In extreme cases, when the cleft is wide and extends far forward, the lower part of the nasofrontal process may be seen forming a narrow central plate partly filling up the cleft between the maxillary processes. In the majority of instances both of harelip and of cleft palate, only the soft parts are defective. Very rarely, a median cleft in the lower lip, and even in the lower jaw, may arise from defective union of the inferior maxillary processes.

Minute fistulæ in the neck, connecting the surface of the skin in front of the sternomastoid with the pharynx, may result from imperfect closure of the branchial clefts (Fig. 1); and cysts may arise from unobliterated remnants of these openings. Fissures may also occur, from somewhat analogous causes, in the sternum, in the diaphragm, and in the sides of the thorax.

The parts concerned in the formation of the umbilical cord furnish many malformations. A persistent urachus may lead to a vesical

FIG. 1.

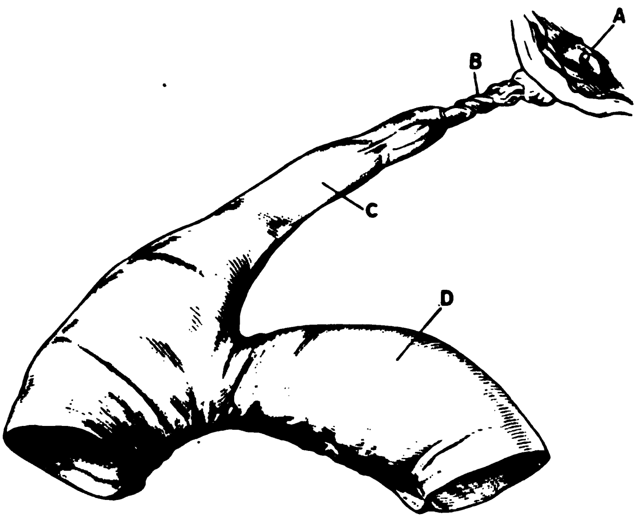


Head of fœtus. (Semi-diagrammatic, and modified from several illustrations from His.) *l. n. pr.*, Lateral nasal process; *m. n. pr.*, mesial nasal process; *max. pr.*, maxillary process; *inf. max. pr.*, inferior maxillary process; *br.* (a), *br.* (b), *br.* (c), the three lower branchial arches. (Waterhouse.)

fistula, and its imperfect obliteration to a cyst in the urachal cord, which then connects the umbilicus and bladder. In the same way a persistent omphalomesenteric duct, which connects the yolk-sac with the alimentary tract, may, in similar fashion, give rise to an intestinal fistula. In most cases, however, the persistent duct merely consists of a pouch arising from the ileum opposite the mesenteric attachment about three feet above the ileocæcal valve. This pouch is similar in structure to the rest of the adjacent intestine and generally forms a simple cul-de-sac two or three inches long (*Meckel's diverticulum*), constituting one of the commonest malformations in the body. More rarely it may attain a length of six inches or upward, and be connected by a fibrous band with the umbilicus (Fig. 2); only in very exceptional cases does it extend to the umbilicus as a patent tube, and give rise to a fistula. A pouch of peritoneum may project into the umbilical cord, giving rise to a hernia.

Fissures in the abdominal wall are generally situated below the umbilicus. If the lateral plates are defective, amnion, peritoneum, and anterior wall of the bladder may give way, and the mucous surface of the posterior wall of the bladder, with the openings of the ureters,

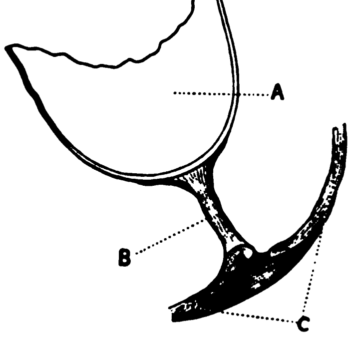
FIG. 2.



Meckel's diverticulum. A, umbilicus; B, impervious fibrous cord; C, diverticulum; D, ileum below diverticulum.

project on the surface (*extroversio vesicæ*). The urethra may remain unclosed, appearing, in the male, as a groove along the dorsum of the penis (*epispadias*), and this condition may be associated with absence of the symphysis pubis and extroversion of the bladder. A commoner deformity is a defective development of the penis, in which that organ is small and grooved on its under surface. The urethra may open at the root of the penis, at the base of the glans, or at any point between these. To these deficiencies are added undescended testicles and a cleft scrotum somewhat resembling the labia majora of the female. This general defective development of the generative organs is known as *hypospadias*, although, strictly speaking, the term should be limited to the urethral malformation.

FIG. 3.



Imperforate anus. A, rectum; B, fibrous cord connecting imperfectly developed rectum and invaginated skin; C, skin.

When the ordinary invagination of the skin to form the anus does not occur, or more commonly when the hind-gut is too short to communicate with the more or less completely invaginated portion of the skin, an

imperforate anus results. The walls of the hind-gut and of the invaginated anus may lie in close contact or may be separated by an interval of several inches (Fig. 3).

Occasionally the hind-gut may be incompletely differentiated from the genito-urinary apparatus owing to the imperfect involution of the allantois, but in such cases the fœtus rarely attains maturity.

Miscellaneous Defects.—The commonest and least important malformation of the **kidney** is an irregularity of the surface due to the persistence of the original lobulations, marking the position of the pyramids—a normal condition in the ox and many other mammals.

Occasionally the lower ends of the kidneys are found united across the bodies of the vertebræ so as to form a horseshoe-shaped organ. The connection may be effected either by fibrous tissue or by ordinary renal tissue. In nearly all cases of horseshoe kidneys the ureters pass downward over the anterior surface, while the arrangement of the bloodvessels is generally somewhat unusual.

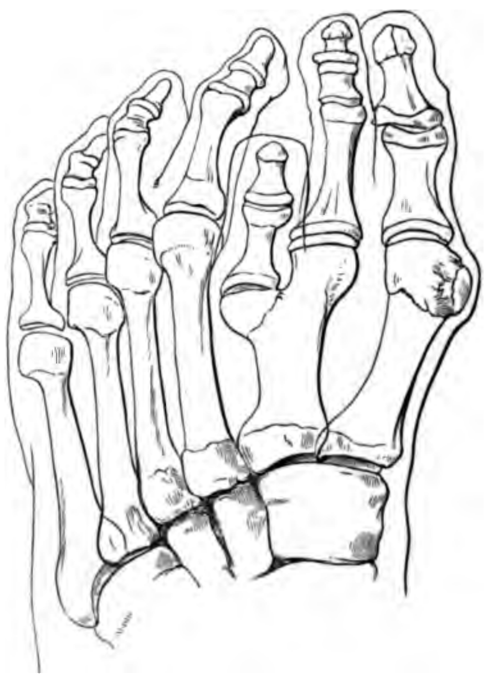
The pelvis of the kidney may be subdivided, and the ureter may be double at its upper part or even throughout its whole length.

On rare occasions the development of one kidney may be so far interfered with that it is at birth represented by a mere fibrous plate; while the opposite kidney is double, or nearly double, its normal size.

Neither **liver** nor **lungs** are liable to any important developmental errors, unless the dilatation of the neighboring bronchial tubes, which results from the inefficient expansion of any part of the lung at birth (*atelectasis*), be regarded as a malformation. (See Bronchiectasis.)

Malformations of the **limbs** are numerous and varied. Those due to excess take the form of giant-growth, in which all the tissues of a limb may be concerned; or of additional parts, as in supernumerary fingers or toes (Fig. 4) and "webbing" of fingers or toes. These two latter deformities are fre-

FIG. 4.



Foot with seven toes. The first two metatarsal bones articulate with the internal cuneiform bone. The third toe has only two phalanges and arises from the second metatarsal bone, the distal end of which is bifurcated.

quently found together, and are often hereditary, occurring in different members of a family.

The absence of limbs may be due to germinal defects, or to intrauterine amputation by amniotic bands at an early period of development. When hands and feet, however imperfect, exist without the intermediate parts, the defect is always germinal.

Congenital dislocations, especially of the hip-joint, are not infrequent, and are associated with defective formation of the joints concerned.

The various forms of congenital club-foot are accompanied by defects in the formation of the tarsal bones, especially of the astragalus, and are possibly due to the pressure exerted by the walls of a misshapen uterus. They are occasionally associated with corresponding cerebral defects.

Malformations of the heart will be considered in the chapter dealing with diseases of that organ.

CHAPTER II.

NUTRITION ARRESTED.

NECROSIS.

THE complete and permanent arrest of nutrition in a part constitutes necrosis, gangrene, or local death.

Etiology.—Whatever interferes with the supply of nutritive material to a part, or destroys the vital activity of its cellular elements, may cause its death.

A. INTERFERENCE WITH THE SUPPLY OF NUTRITIVE MATERIAL.—Such interference may be the result of:

1. **Obstruction in the Arteries.**—This is a common cause of necrosis. The obstruction may be caused by compression, by ligature, by rupture,

FIG. 5.

A necrosed patch in the myocardium. At (*d*) where the muscle-fibres have disappeared, the structure consists of the connective-tissue stroma, and the *débris* of necrosed muscle-fibres. At other places engorged bloodvessels and extravasated blood (*b*, *c*) are seen. The muscle-fibres remaining (*a*) have lost their striation. × 150.

by thrombosis, by embolism, or by disease producing thickening of the arterial coats, and consequent narrowing of the lumen of the vessel. If the obstruction be complete and a collateral circulation cannot be established, death of the part quickly ensues.

2. Obstruction in the Capillaries.—Obstruction is often the result of pressure upon, or stretching of, these vessels. This may take place from the accumulation of inflammatory products or of extravasated blood, or from the pressure exercised by new growths. The resulting obstruction to the capillary circulation causes death of the immediately adjacent tissues. As examples of necrosis from this cause may be mentioned: necrosis of the superficial layers of the bone resulting from periostitis, and due to the compression of the capillaries between the bone and the periosteum; the sloughing of tendons in whitlows before the latter are opened; and the formation of ordinary bedsores. When inflammation causes gangrene, this result is aided by the stasis which occurs in the capillaries. Coagulation of blood takes place in the vessels of the necrosed tissue, and thus hemorrhage from gangrenous parts is prevented.

3. Obstruction in the Veins.—Obstruction to the return of blood by the veins is seldom complete enough to arrest nutrition, and is therefore rarely a cause of necrosis. It is when associated with cardiac weakness or obstruction in the arteries that it constitutes an important agent in producing this result; for then the force necessary to drive the blood on through the narrow venous channel is quite inadequate. Gangrene due to these combined causes occurs after ligature of a main artery and its vein, and may follow accidental injury of the vein during the operation of ligature of a large artery, especially in the thigh. It may also result from constriction of a part by a bandage not tight enough to occlude the arteries as well.

When a strangulated or invaginated piece of intestine is released and the circulation is re-established before gangrene has occurred, severe inflammation, leading to gangrene, may ensue. It is of practical importance to note that *inflammation* sets in only on *re-establishment* of the circulation. A much contused and lacerated part may ultimately be killed because the pressure of the effusion from its injured vessels still further impedes the flow through them.

4. Diminished Cardiac Power.—This is never by itself a sufficient cause of necrosis. In cases, however, of excessive general debility, or of disease of the cardiac substance, the consequent diminution in the contractile power of the heart materially aids the foregoing causes in producing a fatal blood-stasis. The arrest of the circulation in senile gangrene (p. 35), and in that form which so often occurs in the tissues of the back in prolonged fever and in chronic exhausting diseases, is in part the result of diminished cardiac power. This arrest in the last-named conditions is usually determined by some injurious irritation of the tissue—in other words, it is a part of an inflammatory process.

B. Destruction of the vital activity of the cellular elements may be caused by:

Physical and Chemical Agencies.—A part may be completely disorganized and lose its vitality as the result of external *violence*, excessive *heat*, or extreme *cold*. Many corrosive *chemicals*, such as acids and caustic alkalies, destroy the life of cells. Putrid urine or foul secretions

from wounds will sometimes destroy the cells like a caustic. Certain diseases have a special tendency to cause necrosis—*e. g.*, diphtheria, carbuncle, noma, "hospital gangrene," and spreading traumatic gangrene. In these conditions the injury to the tissues is due to the chemical action of bacterial products.

These are the several causes of necrosis; but it must be borne in mind that the process is often complex, and due to the combined influence of two or more of them. The liability to necrosis will greatly depend also upon *the power of the tissues to resist injury.* This varies, probably, in different individuals, and, certainly, in different tissues in the same individual—intestine, for example, being much less resistant to injury than skin, and glandular epithelium than connective tissue. Conditions which would lead to the death of a part in which the circulation was already impeded, or in which the vitality of the cellular elements was impaired, would produce no such effect where such local weakness did not obtain. This is well exemplified by senile gangrene; by the formation of ulcers near varicose veins in the legs; and by the necrosis of the tissues of the back from pressure, which so often occurs in conditions of debility, especially in persons who are lethargic, heavy, and imperfectly conscious. For similar reasons, the diabetic, the albuminuric, and the intemperate are peculiarly liable to gangrene.

Varieties.—These generally follow one of two types known as **dry** and **moist** gangrene respectively. There are three conditions which mainly determine into which of these two varieties a given instance will fall. These are (1) the amount of fluid which the tissues involved naturally contain; (2) the extent to which the vessels of the part affected are engorged with blood, and the amount of fluid which is therefore present at the time; and (3) the rapidity of the evaporation from the surface.

Dry gangrene (*mummification*) will therefore occur in those parts in which the tissues naturally contain but little fluid, such as bone, cartilage, and tendon. It will also be frequently associated with such obstructions of the arteries as may occur without any corresponding interference with the circulation in the veins and lymphatics. Dry gangrene, therefore, may result from embolism, from slowly progressing arterial thrombosis, and from the prolonged administration of ergot. Again, free exposure to dry air, slow progress, and the destruction of the epidermis will all, by promoting or permitting evaporation, aid in producing dry gangrene. Under these circumstances, the part, which is pale from the first, gradually dries up and becomes converted into a dark, shrunken mass, undergoing but little further change. The conditions obtaining in dry gangrene are precisely those which render the growth of organisms almost impossible (Fig. 6).

Moist Gangrene.—Under opposite circumstances, a part, consisting largely of muscle and other soft structures, may become rapidly gangrenous, either from an acute inflammation or from venous obstruction combined with a weak arterial supply. When this happens, its tissues

are gorged with an albuminous fluid full of breaking-down red blood-corpuscles. The hæmoglobin of these forms a red solution which soaks into and stains all the tissues. The part is much swollen, of purplish color, and often studded with bullæ containing blood-stained fluid. If such a part is exposed to warm, moist air, septic bacteria quickly grow through the skin, multiply rapidly in the highly putrescible fluid, and

FIG. 6.

Senile gangrene of the great toe, from a case of arterial thrombosis. The toe is shrunken and its epidermis is being exfoliated. At the line of demarcation the skin has retracted (a) and the deeper parts are separating (b).

generate by their action gases—chiefly sulphuretted hydrogen, ammonia, nitrogen, and carbon dioxide—which give rise to the emphysematous crackling so often associated with gangrene. The tissues soften and liquefy, the whole part becomes exceedingly offensive, and its tissues change in color from reddish to brownish or greenish black. For putrefaction to occur it is absolutely essential that septic bacteria be admitted to the part; consequently such changes are met with chiefly in external parts or in those internal parts to which organisms have free access.

When the life of an internal organ or part is destroyed and bacteria are not admitted to it, as in simple infarction, its tissues subsequently undergo degenerative fatty changes, and are ultimately in great measure absorbed.

Course.—Gangrene may be **circumscribed** or **spreading.** *Circumscribed gangrene* implies a *circumscribed cause.* This form is exemplified by the death of tissue resulting from mechanical violence, the actual cautery, or complete stoppage of the circulation. On the other hand, *spreading gangrene* implies a *spreading cause.* Gangrene from arterial thrombosis spreads slowly, as the thrombus spreads and involves other vessels, and has a well-defined margin. The typical *spreading gangrenes* are produced by the action of living organisms, which continually multiply and provide fresh quantities of the irritant, while

they are constantly being carried by the lymph-stream farther into the surrounding tissues.

When the process becomes circumscribed, the dead tissue—*sphacelus*, or *slough*—acts as an irritant to the adjacent living structures, causing more or less inflammation in them. If the slough is aseptic, the inflammation is slight, leading merely to the formation of a layer of fibroid tissue round the dead mass. This occurs especially in internal parts, and is best illustrated by the usual fate of a small simple infarct. When thus encapsuled the dead part ceases to irritate; it becomes decolorized, fatty, infiltrated with phagocytes, which absorb the fatty detritus, and is ultimately converted into a small fibrous scar, which may calcify.

When the slough is superficial it generally putrefies and becomes strongly irritant; but mummification will minimize this. Inflammatory reaction occurs freely in the narrow zone of *living tissue* (*line of demarcation*) surrounding the edges and base of the slough; fibres and all firm connections between the living and dead tissues are softened and eaten through by leucocytes (*suppuration*); and, finally, when this process is complete, the slough is cast off. If the whole thickness of a limb die, the stump left by casting off the sphacelus will be conical; for the soft parts retract somewhat and the bone separates lower down. The less vascular a tissue, the longer will be the time occupied in the separation—*e. g.*, fascia, tendon, bone. If the dead mass be deeply seated and suppuration occur about it, fistulæ—tubular passages through the tissue—will form, leading from it to the surface. Through one or more of these it may ultimately be cast off, as in necrosis of bone. After removal of the slough an ulcerated surface is left.

Senile Gangrene.

This is a form of necrosis which affects especially the lower extremities of old people, and is the result of several of those etiological conditions which have already been enumerated.

The most important element in the production of senile gangrene is the presence of *atheromatous* or *calcareous changes in the arteries* of the limb, which greatly diminishes the elasticity and calibre of these vessels, thus hindering the circulation in the part and impairing its nutrition. This is shown by the coldness of feet, cramps, and other abnormal sensations so often experienced by the patient for some time before the gangrene sets in. The slowing of the circulation is usually much increased by defective action of the heart due to atrophy or degeneration of its muscular substance. Thus the contact of the blood with an abnormal vessel-wall is prolonged, and this is sometimes sufficient to cause the formation of a *thrombus* in the artery. (See Thrombosis.) The clot thus formed spreads slowly until it may extend from the foot to the groin. Dry gangrene gradually supervenes. This begins in one toe or in several simultaneously, and extends slowly. It is often surprisingly limited; and even where the thrombus extends into the popliteal artery part of the foot may escape. In other cases, *embolism*

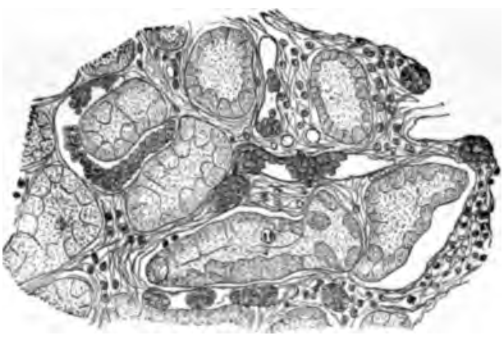
with superadded thrombosis may be the starting-point—a chalky plate or a parietal thrombus being swept from a large into a smaller artery.

The exciting cause of the gangrene is often some trivial injury, such as a slight abrasion of the foot, the cutting of a corn—these slight wounds permitting the entrance of micro-organisms—or some excess of heat or cold, acting upon feebly nourished tissues supplied by diseased vessels.

Coagulation-necrosis.

This is a term applied to a peculiar form of sudden tissue-death. The cells in dying seem to give rise to some substance or substances

FIG. 7.



Necrosis of the kidney from embolism, in a case of aneurism of the abdominal aorta. One of several small yellowish-white patches which were scattered through the cortices of the organs. The cells of the tubules are necrosed and, therefore, unstained, but the connective-tissue cells have taken the stain. The dark masses are red blood-corpuscles. × 200

which unite with the lymph and cause an apparent coagulation of the dying cells. Microscopically, the nucleus disappears, and the contents of the cells are replaced by a structureless hyaline material (Fig. 7). Fatty degeneration subsequently sets in. The process may be the result of bacterial action. It occurs only in parts freely supplied with lymph, and is never found in the brain. S. Martin would confine the term "coagulation-necrosis" to conditions in which cells are killed by the sudden cutting off of their blood-supply, as in cases of embolism of a terminal artery.

Colliquative necrosis is the term employed when the dead tissues do not coagulate, but, as in the case of the brain, soften and liquefy. The cerebrospinal fluid is non-coagulable, and necrosis in the brain is colliquative from the first. In acute pneumonia it follows coagulation, and is due to bacterial products.

Fat-necrosis.

Under the name of *fat-necrosis* a peculiar change occurring in fat has been described. It consists in the formation of opaque white areas, half an inch or less in diameter. These are of firm consistence, and are scattered through otherwise normal fat. They stain with osmic acid and melt on the application of heat. Under the microscope the contents of the affected cells are either crystalline or opaque and granular. The transition from diseased to healthy cells is abrupt (Fig. 8). The surrounding parts are occasionally infiltrated with leucocytes. Fat-

FIG. 8.

Fat-necrosis. The abrupt transition, from the healthy cells on the left to the necrosed cells on the right, is well marked. The contents of the affected cells are finely granular. × 220. (Rolleston.)

necrosis is most frequently encountered in the subperitoneal fat, but is occasionally met with elsewhere. It is probably always associated with disease of the pancreas, and is almost certainly due to absorption of pancreatic juice, which, by means of a special ferment, acts upon the fat and saponifies it.

POST-MORTEM CHANGES.

The changes which always occur in tissues after death must now be considered more particularly. The blood undergoes the earliest and most rapid change. The hæmoglobin escapes from the red corpuscles themselves, and, dissolved in the liquor sanguinis, permeates the surrounding tissues. The corpuscles ultimately disappear, nothing remaining but a few minute granules. The staining of the tissues with hæmoglobin is commonly known as **post-mortem staining,** and the appearances it presents are very characteristic. The lining membrane of the heart and of the bloodvessels, being in immediate contact with the blood after death is the part principally affected. The dissolved hæmo-

globin also soaks through the walls of the veins, thus giving rise, on the surface of the skin, to red lines which mark the position of the vessels lying beneath. The staining is of a uniform pinkish-red color, thus differing from the punctiform and linear redness of hyperæmia, from which it must be carefully distinguished. The amount of staining is in proportion to the rapidity with which decomposition has taken place, and to the amount of blood contained in the part at the time of death. Marked staining of the endocardium and great vessels occurs very rapidly after death from septicæmia.

Post-mortem staining must be distinguished from **post-mortem discoloration.** The latter is a purplish color seen in dependent parts which are not pressed upon, and is due to the gravitation of fluid blood into the vessels of these parts. It disappears if the body be turned over.

In muscle the arrest of nutrition is accompanied by a state of rigidity known as **rigor mortis.** This is a peculiar condition of the muscles observed in almost all bodies after death, in which they become firm and somewhat shortened, as though in a state of permanent contraction. It comes on as soon as the muscles have lost their irritability —*i. e.*, their capability of responding to artificial stimulation; in other words, as soon as the nutritive processes have completely ceased. The time of its appearance will therefore depend upon the state of nutrition of the muscles at the time of death; the more healthy and vigorous this is, the longer will be the interval before nutritive processes completely cease, and consequently the longer before rigor mortis supervenes. Its duration and its intensity are in direct proportion to the lateness of its appearance. In people, for example, who are in perfect health and die suddenly, as from accident, the rigor mortis does not usually come on until from ten to twenty-four hours after death: it is very marked, and often lasts two or three days. In those, on the other hand, who die from some exhausting disease, as from chronic phthisis, in which the nutrition of the muscles has become much impaired, the rigor mortis appears very soon, sometimes as early as ten minutes after death; it is very slight, and may pass off in less than an hour. It has been said that in cases of death from lightning, and from some of the severer forms of the adynamic fevers, the rigor mortis is entirely absent. It is doubtful, however, if this is the case: the rigor mortis has probably escaped observation, owing to its early supervention and rapid disappearance.

With regard to the nature of the change, Kühne and others have shown that it is really owing to the coagulation of the muscle-plasma and the formation of a proteid clot—myosin. The coagulation is attended by the liberation of a free acid (sarcolactic). Thus are produced the firmness, hardness, and opacity of the muscle which are together characteristic of rigor mortis. This change is not confined to voluntary muscle; a similar coagulation of the protoplasm takes place after death in all involuntary muscle-fibres.

As soon as **decomposition** commences, rigor mortis disappears. The

transverse striation of the fibres then becomes indistinct, and gives place to irregular rows of granules and fat-molecules. In the meantime the muscle softens, its sarcolemma disappears, and ultimately nothing remains but a soft structureless débris. In adipose tissue the cells diminish in size, owing to the escape of the fluid fat, which diffuses itself throughout the surrounding structures. The fibres of the connective tissue swell, become opaque, and ultimately liquefy. In nerve-fibres the white substance of Schwann coagulates and collects into small drops within the neurilemma. Cartilage, bone, and hair resist the putrefactive process longer than any of the other tissues, and are the least altered by it.

CHAPTER III.

NUTRITION IMPAIRED.

IT has been shown in the preceding chapter that complete and permanent arrest of nutrition in a part causes death, and, therefore, cessation of function. We have now to consider those morbid processes in which *nutrition* is more or less *impaired*, and in which, therefore, there is a proportionate *diminution* of function. Nutrition may be impaired in two ways: in *quantity*, so that waste comes to be in excess of assimilation; or in *quality*, either the food or the metabolism of the cell being abnormal. Excess of waste over assimilation leads simply to **atrophy** or simple diminution in the size of a part or of the whole body. On the other hand, alteration in the chemistry of the cell, or in the quality of the food supplied to it, may lead to **degeneration** of the cell-contents, some abnormal substance appearing in the tissues.

The degenerative product may theoretically be formed, (1) *anabolically*, by the cell from its food-supply; (2) *catabolically*, by abnormal disintegration of the cell-protoplasm; (3) by *ingestion* or *simple deposition* in the cell from the lymph.

There is a growing tendency among pathologists to regard degenerations as largely due to the action of bacterial products (*toxins*). In some forms this has been proved to be the case.

Degenerative processes are generally divided into two groups: the *degenerations* proper and the *infiltrations*. In the **degenerations**, the cell-protoplasm is gradually transformed into some new material. This process is often continued until complete destruction of the histological elements has taken place and all trace of the original structure is lost. In the earlier stages of the process, function is impaired: in the later, it may be completely arrested. In the **infiltrations**, the new material is supposed to be passively deposited from the lymph (calcareous infiltration) or formed by the cells from their food-supply (fatty accumulation).[1] Infiltration is not necessarily followed by destruction of the histological elements, and function is but little interfered with.

The *degenerations* are: fatty, mucoid, colloid, and probably amyloid. *Cloudy swelling* also comes under this heading. The *infiltrations* are: fatty, calcareous, and pigmentary.

I. ATROPHY.

Atrophy must be carefully distinguished from arrested development. It is a *decrease* in the amount of a tissue, owing to diminution either in *size* (*simple atrophy*) or *number* (*numerical atrophy*) of the histological elements of which it is composed. It is attended by loss of weight

[1] The term "infiltration" is unsuitable for such an active process. Passive infiltration probably occurs only in dead or dying cells.

and impairment of function. The two varieties, simple and numerical, are often associated, the latter being an advanced stage of the former.

Simple atrophy is the commonest form, and may affect all tissues, as is well shown in ordinary emaciation (Fig. 9).

The cells of all glands may undergo simple atrophy; they become smaller, and are often finely granular from the presence of molecular fat. Muscular tissue may also atrophy by simple diminution in the size of its primitive fasciculi.

Unless their *vital activity* is exhausted, the shrunken cells are capable of recovery; all that is necessary for their restitution is diminution of waste or increase of assimilation, according as the one or the other is faulty.

Numerical atrophy is often an advanced stage of *simple atrophy.* The elements not only diminish in size, but some actually perish, as is

FIG. 9.

Adipose tissue. A, normal; B, atrophic, from a case of phthisis; *a*, a single fat-cell, with cell-wall, nucleus, and drop of fat. × 300. (Virchow.)

well seen in advanced atrophy of muscle; then restitution is possible only by the production of new elements. In certain tissues—as the spleen, lymphatic glands, and skin—atrophy is due mainly to numerical loss.

Although atrophy in its strict signification consists simply in a diminution in size or in number of the component elements of a tissue, it *is rarely a perfectly simple process*, but is usually associated with more or less *fatty degeneration*. This indicates some qualitative error in the metabolism of the cells. It will be seen subsequently that fatty degeneration arises from causes very similar to those which produce atrophy itself.

All the tissues of which an organ consists may waste; but the term "atrophy" implies, primarily and chiefly, wasting of its characteristic cells, as opposed to the stroma. The vessels and nerves also share in the wasting process. The fibrous constituents are the last to atrophy; indeed, as the higher cells shrink and disappear the connective tissue of the organ tends to *increase* (*replacement fibrosis*)—as in the secondary "scleroses" of the spinal cord. The overgrowth of connective tissue in such cases is probably due to the fact that, owing to the death of the higher cells, a larger blood-supply than before is available for the less specialized tissue. It is also possible that substances formed in the process of degeneration of the higher cells may act as irritants to the connective tissue and provoke its overgrowth.

The **naked-eye** recognition of atrophy is often difficult. Atrophied organs contain less blood, and are drier, paler, tougher, and more fibrous-looking than in health. But the great criterion is the *diminution in weight and size* of an organ; these, however, vary considerably in health—proportionately with the weight and size of the whole body; moreover, they may be small from incomplete development. Again, accumulation of blood and other fluids in an atrophied organ may bring its weight and size up to or beyond the average, although its essential tissue is considerably diminished in amount. The same fallacy may arise from overgrowth of the fibrous stroma of an organ.

Etiology.—Atrophy may be caused by (1) deficiency in the supply of nutriment, (2) diminution of function, (3) exhaustion of the inherited vital energy, or (4) removal of trophic nervous influence.

1. Deficiency in the Supply of Nutriment.—The effect of diminishing the blood-supply to a part will vary, according to the degree of the diminution, from slight atrophy to absolute necrosis.

This cause of atrophy may be brought about in various ways: (1) *By obstruction of the supplying vessels before they enter a part.* Thus pressure of an abdominal aneurism on the spermatic artery may cause atrophy of the testis; and fracture of a long bone, above the point where its nutrient artery enters, may result in wasting of the upper fragment. (2) *By uniform and continuous pressure* which does not compress the veins disproportionately. Thus atrophy, even of bones, results from pressure of aneurisms and tumors; deep fissures are formed in solid organs from pressure of band-like adhesions; atrophy of the kidneys will follow obstruction in the urinary passages; and, rarely, wasting of a testis may be due to pressure of an old hæmatocele or hydrocele. Pressure may also arise within an organ by the appearance of some new growth distending its capsule and pressing on the rest of its contents, or by the formation of bands of contracting cicatricial tissue traversing its interior. The effect of the latter process is seen in cirrhosis of the liver. In all "pressure-atrophies" the constant pressure also acts directly on the cells of the part and thus impairs their powers. (3) *By passive congestion.* The circulation is impeded, as the blood is not returned normally by the veins. Hence there is deficient arterial supply, and atrophy results. This is seen in the passively congested liver of heart disease.

2. Diminution of Function.—Atrophy always causes diminished functional activity; but sometimes diminished functional activity seems to be itself the cause of atrophy (*disuse-atrophy*).

Diminished functional activity of a part implies that the chemical processes in its cells are less active than normal; such cells require less food. How the needs of each tissue influence the vasomotor mechanism is not understood; but the supply is, as a rule, speedily adapted to any variation in the demand. Consequently, tissues will, soon after they have ceased to perform their functions, receive only sufficient material for those chemical processes which still go on in

them. This is insufficient to maintain the mass of protoplasm required to do the full work of the tissue; so some of it atrophies.

Muscles atrophy when they are rendered inactive by chronic disease of joints, by splints, or by paralysis from disease or injury of the nervous system *above* the anterior cornual cells with which they are connected—*i. e.*, by an "upper segment" lesion. When the muscles of a part waste, all its other tissues—nerves, vessels, bones, and skin—suffer ultimately from impaired blood-supply. Thus, in part at least, we may explain wasting of the bone in a stump or limb long kept at rest; the absence of that intermittent pressure, which it is the function of bones to bear, is probably a secondary cause: at all events, increased strain causes hypertrophy of a bone. After removal of the distal part of a limb, the main artery and branches supplying it become smaller and thinner. The rectum dwindles after colotomy to a scarcely pervious cord: in this case the passage of feces over the mucous membrane no doubt acts as a stimulant to its vessels, as well as an excitant of muscular action, and as, after colotomy, the rectum is never distended, its tissues adapt themselves to the empty condition.

3. **Exhaustion of the Inherited Vital Energy.**—After birth, those parts which are no longer required in the altered circulation gradually atrophy. The umbilical arteries and vein become thrombosed up to their first branches, and shrink to a fibrous cord as the clots organize—just like any other vessel cut across or tied. But this does not explain the closure of the ductus venosus or ductus arteriosus, in which the conditions are not favorable to thrombosis. Obliteration of these vessels can at present be spoken of simply as a developmental fact, comparable to closure of the foramen ovale. The Wolffian body disappears as the kidneys develop, and the thymus wastes in the second year. These, perhaps, are examples of atrophy of organs following the development of others better fitted to do the work—illustrating, as it were, the converse of the law that when an organ atrophies or is removed, correlated organs hypertrophy and take on its function. (See Hypertrophy.)

The female generative organs atrophy at from forty-five to fifty years of age, the male somewhat later; the spleen and whole lymphatic system waste after middle life: probably in these cases the vital energy of the cells of the parts concerned is exhausted about the times mentioned, and diminished function is the result—not the cause.

4. **Removal of Trophic Nervous Influence.**—When a muscle is *cut off* from its connection with the *cells in the anterior cornu*, or when these cells are destroyed or seriously injured (*lower-segment lesion*), fatty degeneration of the muscle, a more rapid process than simple atrophy, sets in. Examples of this are afforded by the acute bulbar and spinal paralyses of adults, infantile paralysis, some cases of progressive muscular atrophy, neuritis from any cause, and rupture, contusion, or section of a nerve. Salivary glands waste on section of their nerves. Nerves cut off from their ganglion-cells (of which they are long processes) also degenerate rapidly and waste. In all these cases the inter-

stitial connective tissue increases, and often becomes loaded with fat, as the higher tissue disappears. (See Diseases of Nervous System.)

General Atrophy.

The term **general atrophy** is sometimes employed as a synonym for general wasting of the whole body. In general wasting, the first tissue to atrophy is the subcutaneous adipose tissue; the fat around the viscera, in the omentum, and in other parts follows, then the muscles and glandular organs, and, last of all, the osseous and nervous tissues.

General atrophy may be caused by:

1. **Deficiency in the Supply of Nutriment.**—Thus the following conditions may all be causes of general atrophy: deficient supply of food; obstruction to the passage of food into the stomach or intestines, as in stricture of the œsophagus or pylorus; the defective assimilation which results from the various conditions giving rise to dyspepsia; interference with the absorption of the chyle, from obstruction of the thoracic duct.

2. **Excessive Waste.**—All conditions attended by the loss of large quantities of nutritive material may also be causes of general atrophy. Among these are: continuous hemorrhages; profuse and long-continued suppuration from chronic bone disease or empyema; diarrhœa; and the excretion of large quantities of albumin in Bright's disease or of sugar in diabetes mellitus. The waste from increased tissue-change accompanying acute febrile diseases must also be included under this head.

3. **Action of Poisons.**—In children who are the subjects of congenital syphilis very marked wasting of all the tissues may occur, apart from such causes as vomiting or diarrhœa. This wasting appears to be analogous to the local atrophies of the nervous system (tabes dorsalis, etc.), which are caused by syphilis, and to be due to the direct action of the virus of the disease.

Although general atrophy may occasionally be referred to one of the foregoing causes, it is usually due to the combined influence of two or more of them. The atrophy associated with pulmonary tuberculosis, for example, results partly from *loss of nutritive material* in profuse expectoration and diarrhœa, partly from *deficient supply* consequent upon imperfect oxidation of the blood and upon interference with assimilation which is so often caused by structural changes in the stomach and intestines, and partly from the *increased tissue-waste* of fever. In the wasting of old age, in addition to the general diminution of nutritive activity, there is frequently some condition of the digestive organs which interferes with assimilation; this materially aids in producing the ultimate result. Increased tissue-waste, loss of appetite, and interference with assimilation all help to produce the atrophy which accompanies fever.

Atrophy of Bone.

As in other tissues, atrophy of bone is usually accompanied by more or less fatty degeneration. *Old age*, *disuse*, and *constant pressure* are its most frequent causes.

When due to *old age*, there is diminution in weight, but no change in size. The loss of weight is the result of the gradual conversion of the compact tissue into one closely resembling the cancellous. The spaces become larger and their bony walls thinner; the consequent brittleness of the bone is therefore a marked feature. This form, known as **eccentric atrophy**, occurs with other senile changes, and generally affects all bones, but is specially marked in the neck of the femur, rendering it liable to fracture from trivial injuries.

Atrophy from *disuse* or from *constant pressure* is accompanied by diminution in size as well as in weight. The bone beneath the periosteum is gradually absorbed, and the medullary canal shrinks proportionately. This variety is known as **concentric atrophy**, but the changes characteristic of the *eccentric* form are often present as well. It is a local alteration, and is met with especially in the long bones, in cases of long-standing ankylosis, dislocation, or paralysis. The effect of constant pressure in the production of atrophy is well shown in the enlargement of clefts and perforations of the hard palate which often results from the insertion of plugs. These interfere with the blood-supply and thus cause atrophy.

Atrophy of bone must not be confounded with *arrested development*. The latter is commonly met with in the later stages of infantile paralysis. A very similar result may be produced by anything which causes premature ossification of an epiphysis, such as rickets, inflammation, or injury. These are the common causes of stunted limbs.

II. DEGENERATIONS.

The degenerations (p. 40) may be advantageously arranged in three groups: (1) *cloudy swelling and fatty changes*, including fatty infiltration (accumulation) and fatty degeneration; (2) *mucoid, colloid, hyaline, and amyloid degenerations*, resembling one another in the transparent structureless character of the degenerative product; and (3) *calcareous infiltration and pigmentary changes*.

CLOUDY SWELLING.

Cloudy swelling, sometimes known as *parenchymatous* or *granular degeneration*, or *albuminous infiltration*, is a frequent change, being found in all diseases attended by considerable pyrexia. Wickham Legg and Liebermeister produced it by subjecting animals to a high external temperature; they therefore regarded the change as due simply to the fever, which, in their opinion, caused increased destruction of proteid. Against this view it may be urged: (1) that increased destruction of tissue may itself produce the elevation of temperature; (2) that the change is less marked in long-continued fevers than in the relatively short fevers of the acute specific diseases; and (3) that the degeneration is specially pronounced in severe cases of diphtheria, in

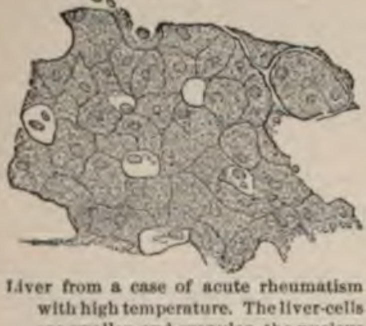
which disease the temperature is often low. All this leads to the belief that mere rise of temperature is not the most active cause. A more probable explanation is that the infective material in the blood—the cause of the fever—has a more or less deleterious action on the tissues. This is supported by the observation that cloudy swelling is the first change noticeable in poisoning by phosphorus, arsenic, and the mineral acids, all of which lead ultimately to fatty degeneration of protoplasm. Again, cloudy swelling is found in inflamed parts; and we shall see later that inflammation is always due to the action of an irritant, which, if it were of sufficient intensity, would produce death of the tissue. It would appear, therefore, that *cloudy swelling is due to the action upon the tissues of some poison which tends to cause their death:* elevation of the temperature of protoplasm above the normal may assist its action.

In considering the histology of this change, we shall find that advanced cloudy swelling passes insensibly into fatty degeneration: it is, therefore, to be regarded as *the first step toward fatty degeneration.*

Seats.—The liver, kidneys, heart, and voluntary muscles show the change most plainly; but probably all protoplasm suffers. The change may be much more advanced in some organs than in others, owing probably to some special stress to which the organs most affected have been subjected.

Appearances.—1. **Microscopic.**—The cells in unstained specimens are swollen and their protoplasm is finely granular, the nucleus and any cell-structure being obscure or even indistinguishable: the granules, which first appear like a precipitate in the cells, refract light but feebly; they are unstained by osmic acid; they dissolve in dilute acetic acid but not in ether, and are therefore albuminous (Fig. 10). In advanced cases, larger, strongly refracting granules, blackening with osmic acid, and soluble in ether but not in acetic acid—therefore fatty—are found associated with the albuminous granules. The affected organs recover in those cases in which the primary disease does not prove fatal, although many individual cells may die and disappear.

FIG. 10.



Liver from a case of acute rheumatism with high temperature. The liver-cells are swollen and granular, the nucleus in many being almost indistinguishable. × 200.

2. **Naked Eye.**—When the change is well marked, the affected organs are somewhat swollen, and may be either anæmic or slightly hyperæmic; the surface of a section bulges a little; and the tissue is softer and more opaque than natural.

Effects.—This change is a sign of the impaired health of the cells: their vital activity will therefore be proportionately affected. Its most serious effect is upon the heart-muscle: the vigor of the contraction is always much impaired.

The Kidneys.—The cortex is principally affected. The Malpighian bodies and the pyramids are usually hyperæmic, and contrast with the general pallor of the cortex. The tubal epithelium presents the appearances described above; they are well seen in the early stages of scarlatinal nephritis.

Fig. 11.

Muscular tissue of the heart, from a case of severe typhoid fever. The fibres are granular, the nuclei obscured, and the striation, at places, entirely lost. × 400.

The Heart.—The walls of the heart become pale and soft. The muscular fibres are finely granular, and have, in many places, lost their distinct striation (Fig. 11).

The Lungs.—The change cannot be recognized by the naked eye. The epithelial cells, according to Buhl, are swollen and granular from the presence of albuminous and fatty particles, and are easily detached from the alveolar walls.

FATTY CHANGES.

The abnormal appearance of fat in the tissues may result from either accumulation (infiltration) or degeneration. Examples of both occur in health (pp. 49, 55).

According to Cohnheim, all fat found in the body has the same chemical composition—being a mixture of tripalmitin, triolein, and tristearin. It does not, however, follow that it is not liable to special and exceptional modifications, particularly in the case of fatty accumulation; for if dogs are fed on colza-oil, linseed-oil, or mutton-fat, the melting-point of the deposited fat will vary with that of the form in which it was given; while in the case of the colza-oil diet the tissues will contain erucic acid, which under ordinary conditions is absent.

I. FATTY ACCUMULATION.

In fatty accumulation, fat brought by the blood is taken up and deposited in the substance of certain cells, especially those of (1) *connective tissue*, (2) the *medulla* of limb-bones, and (3), to a less extent, those of the *liver*. These serve, physiologically, as reservoirs of fat. It is impossible to draw any line between normal and pathological fatty accumulation so long as the process is confined to those cell-groups which are physiologically liable to this change. Thus the subcutaneous fat and the fat normally present on the surface of the heart, along the coronary vessels, in middle-aged adults varies much in amount consistently with perfect health. But when the fat spreads widely over the

surface of the heart it is clearly abnormal; and the evidence of disease is still stronger when the fat appears between the muscular fibres in cells which normally contain none. The tendency to morbid fatty accumulation may be **general** (*obesity*) or **local.**

Causes.—1. Excess of Food.—It may be stated generally that, whenever nutritive material is present in the blood in excess of the amount required for the supply of force and maintenance of heat in the body, there is a tendency to the deposit (storage) of fat, first in regions in which it is normally present, and later in parts which usually contain none. For this, *fat* itself need not be present in excess in the food; the presence of *carbohydrates* in quantity sufficient to satisfy the wants of the organism will protect fat from oxidation and lead to its deposition. The *proteids* of the food may also be split into nitrogenous and non-nitrogenous factors, and from the latter of these fat may be formed.

2. Inherited Tendency.—Nothing is more certain than that a tendency to obesity or to leanness runs in families; and it is notorious that some very stout people are small eaters and take active exercise, whilst many thin subjects are just the reverse. Cohnheim has, it is true, advanced the hypothesis that, in the former, oxidation is naturally slow and imperfect, but we know of no experimental facts in support of the view.

3. Disordered Metabolism.—This may result from sedentary and luxurious habits, lassitude of mind and body, high external temperature, destruction of much lung-tissue by chronic disease, or reduction of the oxygen-carrying power of the blood owing to diminution of red corpuscles or of their hæmoglobin. Some suppose that the fat con-

FIG. 12.

Fatty accumulation in connective tissue. Showing the accumulation of fat within the cells. × 300. (Rindfleisch.)

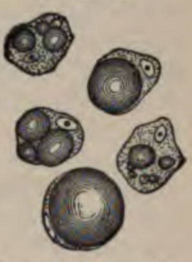
tained in a normal diet may under such circumstances be incompletely oxidized; and that oxidation may be diminished by slow circulation or by the circulation of deoxidized blood through a part—conditions which normally obtain in the liver and in parts thrown out of work—as in a

muscle kept at rest. There is, however, no adequate proof of this. Excess of fat may sometimes be present in the fluids around certain cells—*e. g.*, the liver-cells after a meal containing much fat, and the connective-tissue cells and wandering cells near a focus of fatty degeneration.

Appearances.—1. Microscopic.—Cells in which fat is accumulating are seen to contain droplets of oil—very small at first, but still distinct droplets (Fig. 12). These run together, push the cell-nucleus aside, and distend the cell until its original contents seem to have become a mere capsule to the fat (Fig. 13). As the fat is added to the previous cell-contents, the cell is enlarged in proportion to the amount of fat it contains.

2. Naked Eye.—An organ in which fat has accumulated is more or less swollen. Any sharp edges it may possess tend to become thick and rounded. It is more or less pale and yellowish on account of anæmia (from increased intracapsular pressure) and the presence of fat; it is doughy and inelastic, and both receives and retains an impression from the pressure of a finger; and it is softer than natural. But, except mechanically, the fat need not appreciably hinder the protoplasm of the organ from discharging its functions. Ultimately, however, pressure upon the cells proper may become so severe that they may fail to get sufficient nourishment; they will then undergo fatty degeneration and atrophy. The knife used to cut a fatty organ becomes greasy, and may show distinct drops of oil on the blade.

FIG. 13.



Liver-cells in various stages of fatty accumulation. × 300. (Rindfleisch.)

Seats.—The parts affected are those physiologically liable to the process—viz., *connective-tissue cells* and *liver-cells:* with regard to the former, it is to be noted that normally the cells of the interstitial connective tissue of working organs (muscles, nerves, and glands) are not affected, but may become so, especially if the activity of the organ is in any way arrested. In **obesity**—the commonest manifestation of morbid fatty accumulation—the subcutaneous and subperitoneal connective tissues suffer earliest and most, the accumulation spreading later to the interstitial connective tissue of organs in which metabolism is still apparently normal, as in the heart.

II. FATTY DEGENERATION.

This differs from fatty accumulation, inasmuch as the fat is formed by changes in the protoplasm of the cells themselves. There is reason to believe that cell-protoplasm takes up oxygen and splits into a nitrogenous molecule, which is the first stage in the formation of urea, and a non-nitrogenous molecule which forms fat. In the process of healthy nutrition, these products of the metabolism of the cell are still further

oxidized and then removed. Consequently, we do not, except in the case of the intestinal epithelium and the liver-cells, find fat-granules in healthy cells. When, however, a whole cell or many cells die and are protected from ferments, evidence of fatty degeneration of protoplasm is soon forthcoming. This we can watch in various physiological processes—*e. g.*, the formation of sebum and cerumen. In both of these the fatty degeneration, death, casting off, and disintegration of superficial cells, and the constant production of new ones in the deeper layers, play a chief part. Evidence of the same process is seen in the fatty degeneration of the muscular fibres of the uterus undergoing involution. It was formerly supposed that the transformation of entire bodies, which have lain for many weeks or months in water or damp soil, into *adipocere*—a soap formed by the combination of fat with ammonia and lime—was an illustration of the same process, but this change is now generally believed to be due to the action of micro-organisms.

It is now universally recognized that the fat seen in the muscular fibres in fatty degeneration is the result of a change in the fibres themselves, and is not derived from without. The experiments of Voit and Bauer prove this. These experiments were made to determine the source of the fat in the acute fatty degeneration produced by poisoning with phosphorus. Dogs were starved for twelve days, so that all available fat, whether in the tissues or in the food, might be exhausted. At this period the daily excretion of nitrogen (urea) averaged eight grammes. Small doses of phosphorus were then given. The average daily excretion of nitrogen at once rose to twenty-four grammes, while the amount of oxygen taken up, and that of carbon dioxide given off, were greatly diminished. The animals were then killed, and large quantities of fat were found throughout the body. The increase in the excretion of urea showed that the destruction of proteids was also increased; and the presence of the large quantities of fat found after death made it highly probable that it had been formed as part of the general proteid destruction. In other words, the phosphorus produced very extensive and general fatty degeneration, and the *fat must have arisen from the protoplasm of the cells.* Voit concluded from these investigations (1) that the transformation of cell-proteid is independent of the supply of oxygen, but that if oxygen be deficient, the fat and other products of the transformation, being incompletely oxidized, accumulate in the cell; (2) that the presence of fat in the cells may thus be due to increased transformation of the proteid matter, or to diminished oxidation of the products of its decomposition; and (3) that the fatty degeneration in poisoning by phosphorus is due both to an increased transformation of the cell-proteid and to diminished oxidation of the fat and other products of the transformation.

On the other hand, experiments were made by Rosenfeld, whose results have been confirmed by others, tending to show that the fat found in liver-cells as a result of phloridzin-poisoning is taken up by these cells from the blood and is not formed by breaking down of the cell-protoplasm itself. Rosenfeld starved dogs till all their fat had disappeared, and then by feeding them with tallow caused this abnor-

mal form of fat to be stored up in the adipose tissue in the place of the normal kind. On administering phloridzin to dogs thus treated, it was found that the liver-cells contained tallow in place of the fat normally produced in dogs by the action of this poison: this tallow must have been taken by the liver-cells from other parts, being conveyed to them by the blood-stream. It must therefore be admitted that our views on the subject of fatty degeneration may need revision; but at present there is scarcely sufficient evidence to overthrow the accepted theory.

Stolnikow and Gaule have published experiments which seem to show that fat can be produced by the decomposition of *lecithin*, the phosphuretted fat of the nervous system, and a constituent of many other tissues. According to these observers, glycerophosphoric acid, stearic acid, and cholin are formed in the process.

Etiology.—Fat being a possible intermediate product in the metabolism of a cell, its presence in an unusual situation indicates some incompleteness of, or disturbance in, the metabolism. This alteration in metabolism is due either (I.) to the insufficiency of the supply of nutriment to meet the demand of the cell, the protoplasm of which consequently breaks down; or (II.) to the inability of the cell to utilize the food placed at its disposal.

I. The insufficiency of the supply may be due to primary defects in the supply itself or to an unusual increase in the demand. (1) *The normal blood-supply may be simply diminished*, as in chronic arterio-sclerotic changes in the coronary arteries, causing narrowing of their lumen and consequent diminution of the supply of blood to the muscle-cells of the heart. (2) *Increased work may fall upon the cells without any corresponding increase in their blood-supply.* Thus the fibres of a much hypertrophied heart may undergo fatty degeneration because the coronary arteries—themselves free from disease—are unable to furnish the requisite supply of nutriment. This cause is also possibly operative in the fatty degeneration occurring in febrile states, as increased temperature promotes disintegration of the cells, while no additional supply of food reaches the tissues; but here the action of poisons cannot be excluded. (3) *Actual deficiencies in the blood may impair its nutritive value.* In this case the change principally consists in a marked diminution in the corpuscles and especially in the hæmoglobin, and, therefore, in the oxygen-carrying power. The fatty degeneration is most marked in pernicious anæmia, in which the total volume of blood is much diminished. In these cases there is but little tendency to fatty degeneration in those parts which can be kept in comparative rest; for anæmia, while seriously interfering with the reserve power, is rarely intense enough to diminish the respiratory exchange usual during rest.

II. The failure of the cell to make use of the material placed at its disposal is probably the more important cause. (1) This may be the result of the action of *bacterial toxins*, such as that of diphtheria, which causes fatty degeneration of voluntary muscle-fibres, including those of

the heart; or that of tubercle, which leads to a corresponding degeneration of the affected cells. (2) It may also depend upon the influence of *inorganic poisons*, such as phosphorus, arsenic, alcohol, and carbon monoxide, which act directly upon the protoplasm, and possibly, according to some pathologists, prevent in some way the storage of oxygen. (3) In many cases, the failure of the cell must be regarded as a *senile change* and dependent upon exhaustion of the inherited vital capacities of the cell. This is possibly a factor in the fatty degeneration of cancer-cells, which may occur independently of any limitation of blood-supply.

Appearances.—1. Microscopic.—The microscope is necessary for the recognition of the earliest stages of this degeneration. The fat appears as minute granules, first of all in the protoplasm of the affected cells and later on in the nucleus. The granules—characterized by their sharp contour, strong refractive power, staining-reaction (black with osmic acid), insolubility in acetic acid, and solubility in ether—gradually increase in number, till the whole of the protoplasm may be transformed; some of them may coalesce and form distinct droplets of fat. As the process advances the cells increase in size and become more globular in shape; a little later, the nucleus is involved, the cell-wall, when this exists, is destroyed, and the cell is converted into a mass of fat-granules known as a granule-cell (Fig. 14).

FIG. 14.

Fatty degeneration of cells. *a*, from a cancer; *b*, from the brain in chronic softening. × 200.

Granule-cells may be of two kinds: (1) dead or dying cells converted into masses of cohering fat-granules, or (2) living leucocytes (*granule-carriers*) which have taken up fat-granules from a focus of degeneration—probably to convey them into the lymphatics and thus effect absorption. Connective tissue and neuroglia-cells near foci of degeneration similarly become charged with fat-granules. *Fatty granules* may be distinguished from the *albuminous granules* of cloudy swelling by their larger size, their higher refractive power, their insolubility in acetic acid, their solubility in ether, and their staining-reaction with osmic acid.

2. Naked Eye.—In advanced stages fatty degeneration produces definite naked-eye appearances. These are: (1) slight or moderate swelling, which however is often replaced by more or less shrinking of the organ when absorption of the fat is going on, as in advanced acute atrophy of the liver; (2) admixture of an opaque yellow color with the normal tint of the tissue, often in the form of patches, spots, or streaks, as extreme degrees of the change are usually reached only in limited areas; and (3) loss of elasticity with diminished consistence—the organ being flabby and friable, and its capsule wrinkling easily. When a section is cut, fat may be found upon the knife, and the normal distinctness of the structure is obscured.

Terminations.—1. Absorption.—The fatty particles into which the cells have been transformed are, under favorable circumstances, readily absorbed. The degenerative process may cease and the fat be removed before the part has been dangerously involved. Such recovery probably occurs frequently—for example, in the kidneys and heart. Also when the elements are completely degenerated the fatty debris is usually removed by absorption. This is seen in the fatty degeneration and absorption of the inflammatory products occurring in croupous pneumonia; in the degeneration and absorption of the cells of new-growths—leading to central "cupping" or "umbilication" of nodules, or to shrinking of the whole mass (atrophic scirrhus); and in the degeneration of small damaged areas, such as result from embolism, thrombosis, or hemorrhage in the brain or other organ. As the result of such absorption there may be left a meshwork of vessels and connective tissue from which the essential cells have disappeared, as in the later (red) stage of acute yellow atrophy of the liver; or there may be an ordinary scar, from the development of fibrous tissue; or, lastly, a cavity containing clear fluid may remain. For absorption to occur, the tissues round the degenerated cells must be freely supplied with blood.

2. Caseation.—In this mode of termination the fatty products are not absorbed, but are gradually converted into a yellowish friable material, which has been compared to soft cheese. It is generally said to result from disproportion between the degenerated mass and the vessels by which absorption might be effected—a disproportion which is, in the first instance, the principal cause of the degeneration. It is most frequent, therefore, in parts which contain but few vessels, or in which the vessels become obliterated by pressure from without, or by narrowing of their lumen by endarteritis. Caseation is, consequently, most often met with in tubercular and gummatous masses, and in rapidly growing carcinomata and sarcomata.

Cheesy masses are constantly met with in the lymphatic glands, the brain, the bones, and especially in the lungs. Considerable confusion has arisen as to their nature and origin. Formerly all cheesy masses were regarded as essentially tubercular, and it is true that tubercular lesions have a greater tendency than any others to caseate fully, and to form *typical* cheesy collections. (See Tuberculosis.) But, as just stated, other formations may undergo a change which is practically indistinguishable; so caseation cannot be regarded as proving more than the previous occurrence of fatty degeneration. A caseous mass is tubercular only when it is due to the presence of the *Bacillus tuberculosis*.

The process consists in a gradual drying up of the degenerated elements; the fluids are absorbed, the cells—many of which are incompletely degenerated—shrivel and atrophy, the fat undergoes partial saponification, cholesterin forms, and the tissue thus becomes converted into a soft, yellowish-white cheesy substance, composed of atrophied cells, fatty débris, and cholesterin-crystals. This cheesy material may gradually dry up more and more, and ultimately become

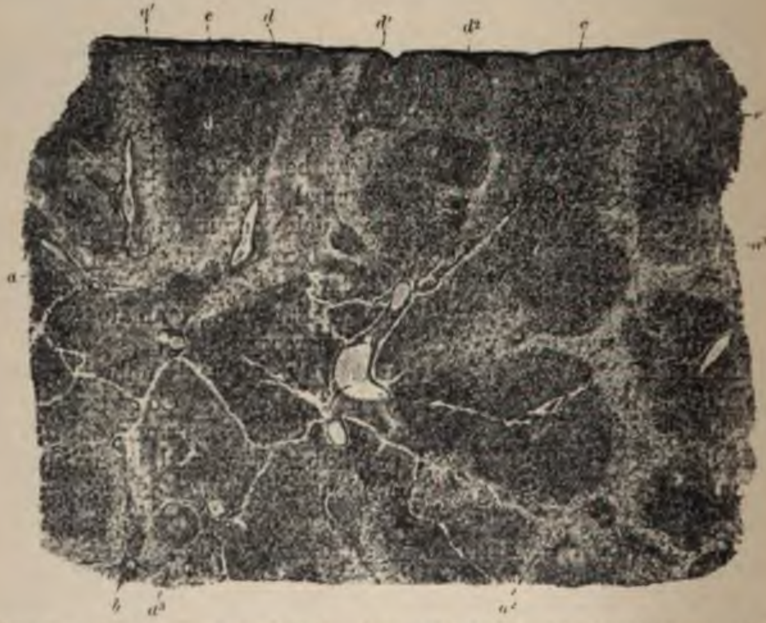
encapsuled by a layer of fibrous tissue, and even calcified. In other cases it may undergo a process of softening and liquefaction. (See Calcification, and Chronic Abscess.)

Results.—The effect of fatty degeneration is to impair, and sometimes, as in the case of the heart, even to arrest function. Recovery is possible only in the earlier stages.

Fatty Accumulation in the Liver.

In the liver fatty accumulation is exceedingly frequent, constituting what is commonly known as the *fatty liver*. This is largely due (1) to the excess of fat and carbohydrates in the portal blood; (2) to the deposition of fat from the metabolism of proteid during the formation of urea; and (3) to the low pressure and slow circulation in the portal vessels—conditions least favorable to metabolism, and most favorable to deposition. An accumulation of fat in the liver may occur under

FIG. 15.



Fatty liver. From a case of general tuberculosis. The fat is unstained, and is represented by the pale areas in the periphery of the lobules. a, a^1, a^2, a^3, fat in the peripheral cells; b, small branch of portal canal; c, peritoneal surface; $d, d^1; d^2, d^3$, recent tubercular foci; e, e^1, intralobular veins. × 24.

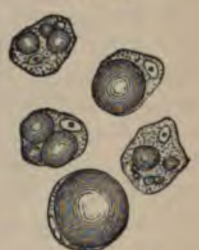
two opposite conditions of nutrition. In the first of these there is *general obesity*, and the excess of fat accumulates in the liver as well as in other parts; in the second there is *general emaciation*, anæmia and other conditions leading to diminution in the nutritive power of the blood and diminished vitality of the liver-cells. The liver in phthisis

is an example of the second of these conditions, the defect in the blood being, in this case, increased by the presence of bacterial products which affect the metabolism of the cells.

Physiological Accumulation.—The liver-cells always contain a small quantity of fat. Ingestion of food rich in fat is followed by a temporary excess of fat in the portal blood, and by the consequent deposition and temporary accumulation of part of this in the liver-cells. This fat is principally deposited in the *peripheral cells* of the lobules—that is, in those which are in immediate contact with the capillaries of the portal vein. After filling these it gradually passes to the central cells. It is ultimately conveyed again into the circulation. This process goes on until the excess of fat is removed from the blood and the cells regain their former character. There is thus a transitory accumulation of fat within the liver-cells, but the vitality of the cells is not impaired thereby.

Pathological Accumulation.—The *fatty liver* is one which constantly contains an abnormal quantity of fat, and here also, as the fat is usually deposited from the blood in the portal capillaries, the increase is first observable in the external zone of the hepatic lobules (Fig. 15). It accumulates within the cells as minute globules which increase, coalesce, and form large drops of fat. These ultimately distend the cells, which become larger and more globular (Fig. 16). As the process advances, the accumulation spreads from the periphery toward the centre of the lobule, until its whole mass may be involved, and all its cells distended with fat. The vitality of the cells is not materially impaired by the change, as is shown by the presence of bile in the intestine and in the gall-bladder. In some exceptional cases the accumulation of fat is most marked around the intralobular veins. In these Virchow suggests that the fat is becoming excreted, and that only the last cells retain a little of it. In cases of extreme fatty accumulation, such as sometimes occurs in persons dying of cancer or phthisis, a section of the liver may look exactly like ordinary adipose tissue, being distinguishable from it only by a faint appearance of a radiating structure here and there, and by the presence of the portal canals and their contained vessels.

FIG. 16.



Liver-cells in various stages of fatty accumulation. $\times 300$. (Rindfleisch.)

To the *naked eye*, the fatty liver is generally increased in size—in advanced stages to perhaps twice the normal. The surface is smooth, the edges are thickened and rounded, and the specific gravity is diminished so that detached portions may float in water, although the absolute weight of the whole organ may be increased. If the accumulation of fat is slight, involving merely the portal zone of the lobules, the cut surface presents a mottled appearance, the external fatty zone being opaque yellowish white, whilst the centre is unaltered, or is hyperæmic and appears as a red spot (*fatty nutmeg-liver*). The more extensive the accumulation the larger is the pale zone, and ultimately, when the whole

lobule is involved, there is left in the centre only a reddish-brown point, marking the position of the intralobular vein. In many cases even this point is lost: then the organ is of an almost uniform opaque yellowish-white color, and the boundary between the individual lobules may be completely obscured. In exceptional cases the accumulation of fat is much more abundant in some portions of the liver than in others, so that on section yellowish points and streaks are seen scattered over its surface. The consistence of the organ is much diminished, it feels doughy, and pits on pressure with the finger, while the knife used to cut it becomes coated with oil. The pressure exercised by the accumulated fat produces considerable anæmia of the organ, but the interference with the circulation is *never sufficient to cause ascites, hemorrhage, or other evidences of portal congestion.*

Fatty Accumulation in Muscle.

1. **Fatty Accumulation in Voluntary Muscle.**—The *cells in the connective tissue* which surrounds the fasciculi of the muscle may become filled with fat: this development of fat *between* the muscular fasciculi (Fig. 17) must not be confounded with degeneration of the fibres themselves. The interstitial fat thus produced varies in amount. In some cases single rows of fat-cells alternate with rows of muscular fasciculi; at other times the accumulation is less regular, more existing between some fibres than between others: in all but the most advanced cases, however, the muscular elements may, under the microscope, be discovered lying amongst the fat—even though to the naked eye the muscle appears to be entirely converted into fat. Ultimately the muscular fibres may undergo true fatty degeneration, and waste until they completely disappear.

This form of fatty accumulation is frequent in *animals* which have been *artificially fattened*—the fat being also increased in the usual situations. It may also occur in *muscles* which from any cause have been *incapacitated* for some time, and in which, consequently, the circulation is reduced to a minimum. Thus it is found in long-standing paralyses from lesions of the brain or cord (upper segment), and in muscles which have been rendered useless by ankylosis of a joint. In progressive muscular atrophy and in chronic lead-poisoning the affected muscles exhibit this change, together with the fatty degeneration.

2. **Fatty Accumulation in the Heart.**—This is not infrequent in general obesity, and after pericarditis followed by adhesion of the two contiguous surfaces of the pericardium. It must be carefully distinguished from the much graver condition of fatty degeneration. In health there is a varying amount of fat beneath the visceral pericardium; it is always most abundant around the vessels in the grooves between the auricles and ventricles. In fatty accumulation this may increase so as to cover the right ventricle, but the left is rarely, if ever, completely enveloped: at the same time the fat may push in along the vessels between the muscular fibres, so that, on the right side, to the naked eye, all appearance of muscular structure may be lost, the walls looking like a layer

of fat, perhaps half an inch thick. In hearts less affected, striæ of fat will be seen lying among the muscle (Fig. 17). The fat is always most abundant near the surface, the muscular structure becoming more evident toward the endocardium: at the base of the ventricles thick villous processes may form.

The interstitial fat displaces and compresses the muscular fibres between which it lies, and diminishes the blood-supply and contractile power of the muscle, perhaps ultimately causing true fatty degeneration of the muscle. The two processes often coexist. Fatty accumulation

FIG. 17.

Fatty accumulation in the heart. A section from the outer part of the left ventricle, showing growth of fat (*f*) *between* the muscular fibres. In some places fatty degeneration is commencing (*d*). × 200.

is probably possible only as the functional activity of the muscle diminishes, and the continued action of the causes leading to this depression would ultimately cause degeneration of the fibres. Fatty degeneration and wasting of muscular fibres, on the other hand, are very likely to be followed by accumulation of fat in the interstitial tissue.

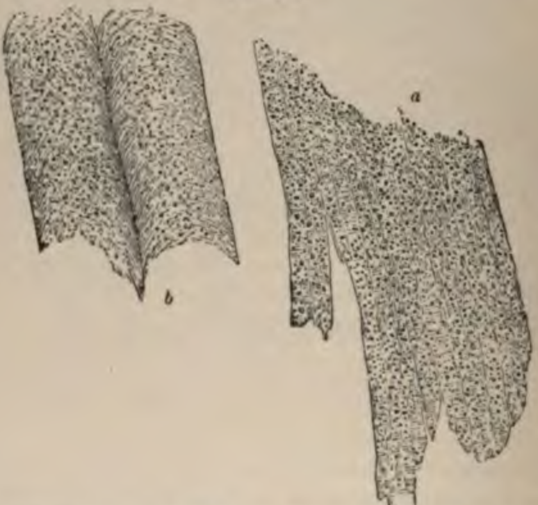
Fatty Degeneration of Muscle.

Both striated and non-striated muscle may be the seat of *fatty degeneration*. In both, the muscle-cells are the seat of the change; they become filled with fat-granules and are ultimately destroyed: the process thus differs essentially from *fatty accumulation*.

1. **Non-striated Muscle.**—Fatty degeneration is frequently met with in the middle coat of arteries undergoing atheroma and in the muscular fibres of a uterus in process of involution.

2. Striated Muscle.—Both the voluntary muscles and the walls of the heart show identical changes. The earliest stage of the affection is characterized by an indistinctness in the transverse markings of the fibres, which in many parts become studded with minute particles of fat (Fig. 18). These gradually increase in number and size, but at first remain small, and are usually distributed somewhat irregularly within the sarcolemma. In some parts single or parallel rows of granules are found running along the length of the fibre; in others they are grouped around the nuclei, which they seem to lengthen, or arranged in transverse lines corresponding with the striæ of the muscle. The fibres become extremely friable, and are readily broken up into short fragments. As the process advances the transverse markings entirely disappear, and nothing but molecular fat and oil-globules are seen within the sarcolemma (Fig. 19). It has recently been affirmed that in some cases the striation is merely obscured by the fat-droplets, and that these are in the early stages confined to the interfibrillary sarcoplasm. The sarcolemma itself may ultimately be destroyed, and

FIG. 18.



Acute fatty degeneration of heart and of other muscles (unstained). From a girl suffering from slight valvular disease of the heart, who died after profuse menstrual hemorrhage and vomiting. *a*, heart; *b*, rectus abdominis. × 400.

nothing remain of the original fibre but the fatty débris into which its albuminous constituents have been converted. This is true "fatty degeneration" of muscle.

This change is seen in muscles paralyzed from "lower segment" lesions, such as progressive muscular atrophy and multiple neuritis.

It is in the **heart**, however, that fatty degeneration of muscle is most frequently met with, and here it assumes a most important aspect from the deleterious influence which it exercises upon the motor power of the organ. The degeneration may be *diffuse* or *circumscribed*; *slight* or *advanced*; *acute* or *chronic*. The wider the extent of tissue that is

affected, the less advanced, as a rule, is the degree of the degeneration. It is in those cases in which only small tracts of tissue are involved that the process is met with in its most advanced stage.

When the change is slight, as in the **diffuse** form, the muscle is somewhat softer and more flabby than natural; it is more friable, and often breaks with a soft granular fracture; while its color is rather paler and more opaque than that of healthy cardiac tissue. The microscope shows the muscular fibres to have lost to some extent their striation, and to contain granules of fat (Figs. 18 and 19).

The diffuse form of degeneration often occurs rapidly and is caused by those general disturbances of metabolism already alluded to (p. 51).

There is no clear line dividing the diffuse from the circumscribed form. Sometimes the degeneration, although more or less general and due to general causes (p. 51), is much more advanced in some parts than in others.

The **circumscribed** form is generally due to *some interference with the circulation in the coronary arteries.* This occurs especially in con-

Fig. 19.

Fatty degeneration of the heart. From a case of pernicious anæmia. The protoplasm is replaced by globules of various sizes stained black by osmic acid. The outlines of the fibres are irregular owing to inequality in their distention. × 400.

nection with aortic incompetence, and explains the early failure of cardiac power in this form of valvular disease. Atheromatous changes at the orifices of these arteries lead in the same way to diffuse fatty degeneration. Adhesive pericarditis and myocarditis act similarly; they hamper the heart mechanically, and the cause of the inflammation acts injuriously on the muscle-cells.

In such cases the heart presents a mottled appearance; opaque, pale yellowish or brownish patches are seen irregularly distributed throughout its substance. These patches, which vary considerably in size and form, are met with especially in the papillary muscles, the columnæ carneæ, and in the layers of fibres immediately beneath

the endocardium. They may also occur beneath the pericardium and in the deeper portions of the organ. They correspond with the most degenerated portions of the tissue. They are flabby, and have a soft consistence, tearing readily under the finger. Under the microscope, the fibres are seen to be in an advanced stage of fatty degeneration, containing particles of fat and oil-globules, which in many parts have escaped and lie free among the surrounding but less degenerated tissues. These more localized degenerations are most common in old people, and usually result from considerable disease of many of the *small* branches of the coronary bloodvessels, and not from conditions of general anæmia. The peripheral layers of the muscular walls also frequently undergo extensive fatty degeneration as the result of pericarditis. The connection between these localized degenerations and the occurrence of rupture or of aneurism of the heart is described in the chapter on Diseases of the Heart.

FIG. 20.

Brown atrophy of the heart, showing the granules of pigment and the atrophy of the fibres. The latter have in some parts undergone slight fatty degeneration. × 400.

Brown Atrophy of the Heart.—Somewhat allied to, and occasionally associated with, fatty degeneration of the heart, is the condition known as brown atrophy or pigmentary degeneration. This consists of a gradual atrophy of the muscular fibres, together with the formation of granules of brownish-yellow or blackish pigment. These granules of pigment, which are probably the coloring-matter of the muscle, are either grouped in clusters around the nuclei or more generally distributed within the fibres. The fibres are frequently, at the same time, the seat of more or less fatty degeneration (Fig. 20). This change usually occurs as a senile one, or as a part of general marasmus from other causes. It is also met with in some cases of cardiac hypertrophy. Its recognition is in most cases impossible without the aid of the microscope.

Fatty Degeneration of Bloodvessels.

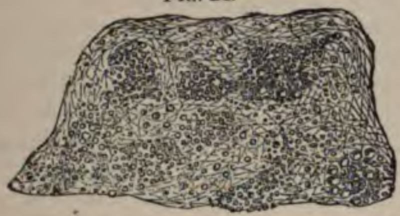
Primary fatty degeneration of bloodvessels is in most cases a senile change, but is not infrequently met with in young and apparently healthy persons. It is then, in all probability, due to deleterious substances in the blood or to some interference with the normal circulation.

Fatty Degeneration of Arteries.—This may be *primary*, or *secondary* to atheroma or other inflammatory condition of the vessels. (See Diseases of Bloodvessels.)

Primary fatty degeneration may affect any or all of the coats of the artery, but is most commonly met with in the *intima*. The change usually commences in the endothelial and subendothelial cells, small groups becoming affected in various parts of the vessel. It may gradually extend from within outward, the intercellular substance softening, until, in exceptional cases, the whole thickness of the intima is destroyed (Fig. 21).

In the earlier stages this condition is recognized by the existence of small, irregular, opaque, yellowish-white patches, projecting very slightly above the surface of the intima. These are often met with on the lining membrane of the aorta. They are in most cases readily distinguishable from atheromatous patches by their superficiality and by the facility with which they can be stripped off from the subjacent layers, which present a natural appearance. In many cases the change

FIG. 21.



Fatty degeneration of the internal coat of the aorta. Small yellowish-white patches were scattered over the lining membrane of the vessel. A very thin layer was peeled off. The groups of fat-globules and their distribution in the intima are shown. × 200.

is limited entirely to the innermost layers of the vessel. The more the subjacent tissues are involved, the greater is the irregularity in the shape of the patches, and the less readily can they be separated with the forceps.

The opaque patches occasionally break down. For this to happen, the cells must become destroyed by the fatty change and the intercellular substance softened. The granular débris thus formed is car-

FIG. 22.

Fatty degeneration of small vessels of the pia mater. From a case of chronic Bright's disease. *a*, a small artery, the coats of which are somewhat thickened; *b*, a capillary, in which are seen a few red blood-corpuscles. × 400.

ried away by the circulation, leaving small, irregular, superficial erosions upon the lining membrane of the vessel. These may eventually heal by proliferation of the marginal cells.

Fatty degeneration is also liable to affect the *media*—especially the muscle-cells (Fig. 22)—and in this situation its injurious influence is most marked. Here, by diminishing the elasticity and contractility of the vessel, it causes degenerative changes in the parts which it sup-

plies, and may even lead to rupture of the affected vessel itself. This is exemplified by many cases of chronic cerebral softening and cerebral hemorrhage, although in such instances atheroma is generally associated with the simple fatty changes. In the larger arteries, as the aorta, it is of much less importance than atheroma, which has a far more deleterious effect.

Fatty Degeneration of Capillaries.—Fatty changes are also found in the capillaries, especially in the nervous centres and the kidneys in Bright's disease (Fig. 22, *b.*). The process commences around the nuclei of the endothelial cells, and may involve considerable areas of the capillary wall, so that rupture is often the ultimate result. This is common in the smallest cerebral bloodvessels, where it is sometimes a cause of cerebral (capillary) hemorrhage. It is said to be present in hæmophilia, and to account for the tendency to hæmorrhage after slight injuries, which is characteristic of the malady.

Fatty Degeneration of the Kidneys.

Fatty degeneration of the kidneys frequently occurs as a result of inflammation of these organs, and accounts for the fatty casts met with in chronic tubal nephritis. It is also met with in acute yellow atrophy of the liver and in chronic wasting diseases, especially in chronic pulmonary tuberculosis. It is a result of phosphorus-poisoning, pernicious anæmia, and amyloid degeneration.

For fatty changes in the tissues of the nervous system, see the chapter on Diseases of Nervous System.

MUCOID DEGENERATION.

Mucoid, *colloid*, *hyaline*, and *amyloid degenerations* resemble one another in the structureless appearance of the new material. The chemical composition of the degenerative product is not absolutely constant in any one of the four. According to some authorities, *hyaline* and *colloid* changes should, for practical purposes, be regarded as identical; for while there is no clear distinction between them, they both include many complex proteid substances resembling one another in their gelatinous consistence. Other pathologists, again, class *hyaline* with *amyloid* degeneration, regarding the former as an early stage of the latter.

In *mucoid degeneration* the affected tissues are transformed into a soft or semifluid substance which, in its final stages, contains mucin.

The *cause* of mucoid degeneration is unknown. Throughout life a mucoid change occurs physiologically in the secretion of mucus; a clear drop of mucus appears in the protoplasm and increases till the cell bursts and the mucus is evacuated, the cell, as a rule, not being destroyed, but remaining as a "goblet-cell." The substance formed under pathological conditions appears not to be absolutely identical with normal mucin. It is found in many cases to be soluble in water, and not to form a precipitate with acetic acid. It has been called "pseudo-mucin."

Seats.—Mucoid degeneration may affect both cells and intercellular substance. It is met with (1) in *catarrh of mucous membranes*, the transformation occurring much more rapidly than under normal conditions, and the cells being often cast off; and (2) as a gradual change in *connective tissue*, in *cartilage* (especially the intervertebral and costal cartilages of old people), in *bone*, and in many *new-growths*, including those of the connective-tissue type, as well as cancers, in which it may affect both cells and matrix. Ovarian tumors may also undergo mucoid degeneration.

Appearances.—*Under the microscope* these are the same as in the physiological process, but the cells are more frequently destroyed. *To the naked eye*, the affected parts are transformed into a homogeneous, colorless material, of a soft, mucilaginous, jelly-like consistence. When the change is limited to isolated portions of the tissue, the softened parts often present the appearance of cysts. These are most frequently met with in the costal cartilages and in new-growths.

Myxœdema, a disease due to atrophy of the thyroid body, was so named on the supposition that the swollen connective tissue characteristic of the disease contained a large quantity of mucin. It has, however, since been shown that at the time of death the proportion of mucin in the skin is only slightly, if at all, in excess of the normal amount. (See Chapter XII.)

COLLOID DEGENERATION.

Colloid degeneration consists in the metamorphosis of cell-protoplasm into a substance known as *colloid*. Chemically, this is said to differ from mucin in containing sulphur and in not being precipitated by acetic acid or alcohol; moreover, it swells when treated with acetic acid. In all probability the name is applied to different substances varying widely in composition.

In the adult, many vesicles of the thyroid gland normally contain some colloid; it is only when the formation of this material becomes general and excessive, producing one form of goitre, that the process is to be regarded as pathological in this organ.

The *cause* of this form of degeneration is unknown.

FIG. 23.

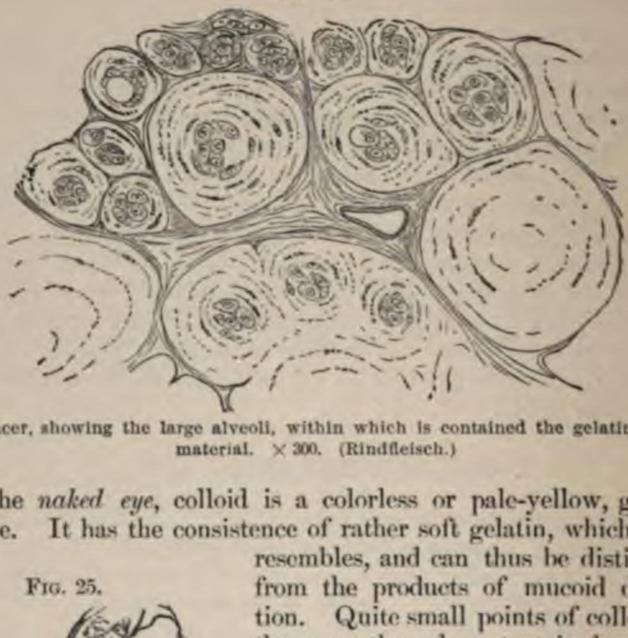
Colloid cells, from a colloid cancer. (Rindfleisch.)

Seats.—Colloid degeneration occurs most frequently in the *thyroid* gland, where, indeed, the "degeneration" appears to represent a pathological secretion; then in certain *new-growths*, both sarcomata and carcinomata (especially of the stomach), the secondary growths undergoing the same change. Ovarian tumors often contain colloid.

Appearances.—*Microscopically*, the first change observed is the appearance of one or two small masses of colloid in a cell (Fig. 23). These coalesce, enlarge, and push aside the nucleus until all the

protoplasm is replaced and the cell is considerably swollen. The nucleus usually atrophies and disappears, but may become colloid. Neighboring cells coalesce into small masses, and these again into larger, which not uncommonly look as if they were concentrically laminated (Fig. 24). Thus cavities full of colloid are formed. The intercellular substance atrophies rather than degenerates, whereas in mucoid degeneration it is frequently affected by the morbid process.

FIG. 24.



Colloid cancer, showing the large alveoli, within which is contained the gelatinous colloid material. × 300. (Rindfleisch.)

To the *naked eye*, colloid is a colorless or pale-yellow, glistening substance. It has the consistence of rather soft gelatin, which it much resembles, and can thus be distinguished from the products of mucoid degeneration. Quite small points of colloid catch the eye: they do not stain brown with iodine, nor rose-red with methyl-violet (p. 67). In advanced stages colloid may soften; and the softened masses, separated by septa of comparatively undegenerated tissue, give the appearance of cysts in a tumor.

FIG. 25.

A portion of the soleus muscle, from a case of typhoid fever, showing two degenerated and one normal muscle-fibres. × 150.

The term "colloid cancer" is applied to growths—generally within the abdominal cavity—which undergo a transformation into soft transparent material: in many cases the change would be better described as "mucoid" degeneration. Change into true colloid material, such as is seen in the thyroid gland, is rare elsewhere, except in metastatic tumors originating in this organ.

Zenker's Degeneration of Muscle.

Seats.—This change is generally regarded as a form of colloid or hyaline degeneration. It was first found by Zenker in the muscles in typhoid fever—chiefly the recti abdominis, adductors of the thigh, the diaphragm- and tongue-muscles. It occurs, though less often, in other infective febrile diseases, such as smallpox and cerebrospinal meningitis; in trichinosis; in abscesses and tumors of muscle; and in the neighborhood of burns and bruises—either before or after systemic death.

Appearances.—*Microscopically*, the altered fibres are much swollen and the transverse striation is lost. The sarcolemmata are occupied by a homogeneous, structureless material, which is exceedingly brittle, and usually presents a wrinkled appearance, or is broken up transversely into irregular fragments (Fig. 25).

The portions of muscle affected are, to the *naked eye*, semi-opaque, pale, slightly lustrous, of a reddish-gray or brownish-yellow color, and abnormally friable. They appear somewhat like the muscles of frogs or of fish. In no part are all the fibres affected. The damaged fibres are regenerated in the usual way. Rupture of the fibres is often associated with hæmorrhage into the substance of the muscle.

Etiology.—Two views are held concerning this change. According to some pathologists, it is a variety of degeneration or coagulation-necrosis in which the muscle-fibres become brittle, and generally rupture. Thus, Babes regards it as a coagulation-necrosis due to the action of the toxins of the typhoid bacillus. According to others, the muscle-fibres rupture from weakening due to granular degeneration or to damage; while the appearances just described are regarded as the ordinary manifestations of tissue-death, as they can be produced experimentally by rupturing the fibres.

HYALINE DEGENERATION.

This term is either used as synonymous with colloid or is reserved for a certain stage in a change peculiar to *arteries* and *connective tissue*, in which the new material is indistinguishable from colloid. Hyaline change is frequently found associated with amyloid degeneration.

Seats.—The chief seats of this change appear to be the arteries of the brain and of lymphatic glands. In arterioles the intima is here and there converted into a shining, thickened layer, giving rise to irregular spindle-shaped enlargements: in larger arteries becoming aneurysmal, the degenerative change follows the increased growth of connective tissue which occurs at the weakened spot. It may also be found in fibrous tissue of inflammatory origin. Hyaline masses may occur in old thrombi, in which they arise apparently by transformation of red blood-corpuscles or fibrin.

When hyaline degeneration occurs in conjunction with amyloid change, it generally seems to be the immediate precursor of the latter.

AMYLOID DEGENERATION.

(Syn.: Waxy, Albuminoid, or Lardaceous Degeneration.)

Amyloid degeneration is characterized by the appearance in the tissues of a firm, colorless, translucent substance, known as *amyloid* or *lardacein*. This substance offers an exceedingly prolonged resistance to gastric digestion and exhibits characteristic staining-reactions.

Seats.—The change is widely distributed. It may be found in almost any organ; those most frequently affected are the **spleen, liver, kidneys, intestines,** and **lymphatic glands.** Less frequently, and especially when the change in the organs just mentioned is advanced, minor degrees of it may be found in the stomach, suprarenal capsules, pharynx, œsophagus, bladder, prostate, generative organs, serous membranes, the membranes of the brain and cord, and muscle. There is no rule as to the order in which the organs are affected. As a **local change,** distinct from the above, it occasionally affects *pathological products,* as old thrombi, inflamed glands, scars (especially syphilitic), and tumors.

Appearances.—*Microscopically,* the morbid substance usually appears first in the subendothelial connective tissue of the **arterioles** and **capillaries** (Figs. 26, 28, 30), and in the media of the former; the endothelium is unaffected and the adventitia usually escapes. The change greatly diminishes the lumen of the vessel; it does not affect the walls of the latter uniformly, but frequently causes spindle-shaped enlargements. The vessels of many parts escape entirely, and the distribution of the change in an affected organ may be quite irregular, while the primary change may even occur in connective tissue apart from the vessels.

With regard to the further spread of the change, all authorities are agreed that the *connective tissue* in every affected organ suffers most, and swells into homogeneous waxy-looking masses which frequently coalesce. Between these the fatty and shrivelled cells of the organ may be seen (Fig. 28). These rarely undergo amyloid degeneration, but it is difficult in degenerated tissues to be certain of the exact cells which have given rise to the new product. In a case of amyloid change in the liver, associated with gummata, the liver-cells appeared to be undergoing the degeneration (Daniel).

FIG. 26.

Fragments of capillaries which have undergone amyloid degeneration. × 300.

Organs in which amyloid degeneration is at all advanced present features so characteristic that its presence can be readily recognized by the *naked eye.* They are considerably and uniformly enlarged, any edges they may possess becoming more or less

rounded. Their absolute weight is increased, and also their specific gravity; their surface is smooth, and the capsule tense and stretched; their consistence is firm and somewhat elastic. On section, they exhibit a peculiar homogeneous, glistening, translucent appearance, somewhat resembling white wax. Owing to the diminished calibre of their blood-vessels and to the pressure exercised by the new material, they contain but little blood, and hence are always pale in color. In slighter degrees of the change, spots and patches of the morbid material may be scattered, like grains of boiled sago, through the affected organs. Although the above characters are sufficiently distinctive in advanced stages, the color-reactions mentioned below should always be used, for they will reveal altered patches—*e. g.*, in intestine—not obvious without them. For the recognition of the degeneration in its *earliest* stage the microscope is also necessary.

Chemical Nature.—By submitting affected organs to gastric digestion, the substance may be obtained almost pure. It has been shown by Krawkow to be composed of an organic acid (chondroitin-sulphuric), combined with some form of albumin. The latter portion of the compound seems to vary in composition.

With regard to its **color-reactions**, the best for *naked-eye* purposes is that with iodine. To obtain this, wash a thin slice of an affected organ, and pour over it a watery solution of iodine, made by diluting the tincture with three times its bulk of water. In this way the amyloid portions are at once stained dark mahogany-brown, the healthy tissues assuming a bright-yellow color. If this surface be treated with a 10 per cent. solution of sulphuric acid, the degenerated parts frequently, but by no means invariably, assume a dark-greenish hue.

The iodine-reaction quickly fades, and, therefore, is useless for permanent preparations. It is occasionally given with other albuminous compounds, and cannot always be obtained in the earliest stages of amyloid degeneration.

For *microscopic* purposes, the most reliable reaction is that obtained by staining the sections with methyl-violet (1 per cent. watery solution). After some hours the amyloid parts are stained bright magenta, and the rest of the tissues blue. Sections must be mounted in glycerin or Farrant's solution, as the color is destroyed by alcohol. This staining is more permanent than that by iodine. In advanced stages of the disease, a useful reaction may be obtained by staining sections with iodine, mounting them in glycerin, and placing at the edge of the cover-glass a very small quantity of strong sulphuric acid: in about twenty-four hours the amyloid tissues will be found stained blue.

Etiology.—Amyloid degeneration is said to be commoner in males than in females, and to originate below the age of thirty. It is almost always *secondary* to prolonged and profuse suppuration, and is commonly associated with chronic tubercular disease of lung, bone, joint, or kidney; with empyemata and septic compound fractures; and, less

frequently, with dysentery, actinomycosis, and the cachexia of tertiary syphilis, especially when there is chronic bone disease. Rarely it appears in the cachexiæ of severe malaria, of leucocythæmia, and of cancer; and very rarely, especially in children, the degeneration may seem to be *primary*.

The degeneration may appear in two to three months, or, under apparently similar circumstances, its onset may be long delayed, especially in young children. Like hectic fever, it occurs much more readily as a result of suppuration in an ill-drained cavity than from a cutaneous ulcer, upon which the pus cannot accumulate under pressure, and from which, therefore, toxins are not so likely to be absorbed.

Lubarsch produced the change experimentally in animals, by exciting and maintaining suppuration by means of cultures of the *Staphylococcus pyogenes aureus*, and proved its presence in a portion of the spleen which he excised. The animals were then allowed to recover from the suppuration and subsequently killed, when the remainder of the spleen was found free from any trace of amyloid degeneration.

According to some unconfirmed observations, the change may also follow suppuration induced by injections of turpentine or of the toxins of the Bacillus pyocyaneus. The variations in the chemical composition and in the staining-affinities of amyloid, and the varied conditions under which it occurs, certainly suggest the possibility of variety in its causation.

Effects.—The diminution of the blood-supply, due to narrowing of the arterioles combined with the direct pressure of the new material, causes the atrophy and fatty degeneration of the essential cells which nearly always occur in organs undergoing amyloid degeneration. The change in the vessel-walls alters the quantity and quality of the transudation, as is shown by the changes in the urine when the kidneys are affected.

Removal of the cause—*e. g.*, chronic suppuration—of amyloid degeneration may lead to arrest of the deposit and to its disappearance from the diseased organs, even in marked cases; but in the great majority of instances the change is steadily progressive, and terminates fatally.

Pathology.—Krawkow obtained a compound very similar to amyloid from the normal aorta of a horse, as well as from cartilage and the organic framework of bone, so that, as in other cases, it is possible that amyloid degeneration has a physiological prototype.

From the facts already cited, it is highly probable that the degenerative product in amyloid disease is not always exactly the same, and that it cannot always be sharply marked off from the products of other degenerations. The experiments of Lubarsch and others, quoted above, show that the disease may be due to the presence of the toxins of the Staphylococcus pyogenes aureus. It is further probable that the degeneration is always due to the action of some bacillary toxin which affects

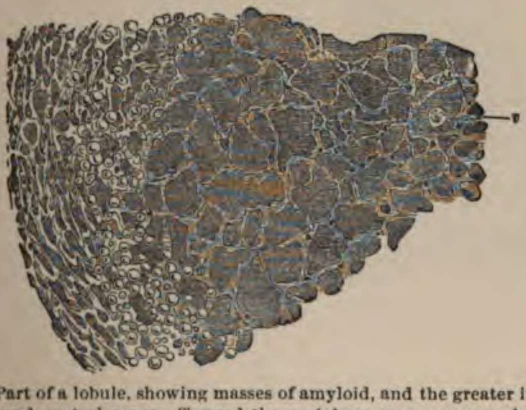
the metabolism of the cells, and leads to the formation and deposition of unusual derivatives of albumin. The disease is usually classed among the degenerations (p. 40); some authors, however, maintain that amyloid material is formed by metamorphosis of red blood-corpuscles, and is in reality an infiltration from the bloodvessels.

Amyloid Degeneration of the Liver.

Microscopically, the earliest changes are observed in the walls of the capillaries and arterioles of the hepatic artery; and, very rarely, in the capillaries of the portal vein. Thence the deposit spreads to the intralobular connective tissue round the affected vessels, ultimately reaching and affecting the tissue between the lobules and leading to confusion of their outlines. The connective tissue swells into homogeneous columns which split readily into flakes, somewhat suggestive, under a low power, of masses of degenerated liver-cells or even of whole lobules (Fig. 27). Careful examination (p. 67), however, reveals, between the amyloid masses, the liver-cells more or less atrophied and pigmented, the peripheral cells, especially, being infiltrated with fat (Fig. 28).

To the *naked eye,* the amyloid liver possesses the typical characters already described (p. 66). If the change is very far advanced, the

FIG. 27.



Amyloid liver. Part of a lobule, showing masses of amyloid, and the greater implication of the intermediate and central zones. Toward the periphery are seen a number of fat-globules, a certain amount of fatty accumulation being associated with the amyloid change. *v*, Intralobular vein. × 100.

tissue may be perfectly homogeneous, all distinction between the individual lobules being lost. In other cases the lobules are distinctly mapped out; they are enlarged, and the external zone may be of an opaque yellowish-white color owing to the presence of fat. This association of the fatty and amyloid changes is exceedingly common. Amyloid degeneration does not obstruct the portal circulation, and hence does not cause ascites (see "Cirrhosis of Liver"), except in those rare cases in which the portal vessels are involved. It causes fatty degen-

eration and atrophy of the hepatic cells, and thus interferes with the functions of the organ.

FIG. 28.

Amyloid degeneration of liver, showing the fatty shrunken liver-cells full of dark granules. The paler homogeneous masses are the swollen capillaries which have undergone amyloid degeneration. In two places the nuclei of the cells forming the walls of the capillaries are visible. × 650.

If sections are stained with iodine, the mahogany color will frequently be found limited to the so-called "intermediate zone" of the lobules—the area of distribution of the hepatic artery. The appearance thus produced is that of a number of partially compressed rings with pale centres, and still paler intervening spaces (Fig. 29). Thus the earliest seat of amyloid degeneration differs from that of fatty infiltration, in which the fat first accumulates in the cells of the outer or portal zone (Fig. 15), and from that of passive congestion, in which the changes begin in the central zone around the intralobular vein. All these changes not uncommonly occur together. As the amyloid change advances, first the central zone and later on the peripheral zone are affected, and even the interlobular connective tissue may ultimately become involved.

FIG. 29.

Amyloid liver. Stained with iodine. The darkest portions represent the affected intermediate zones. Natural size.

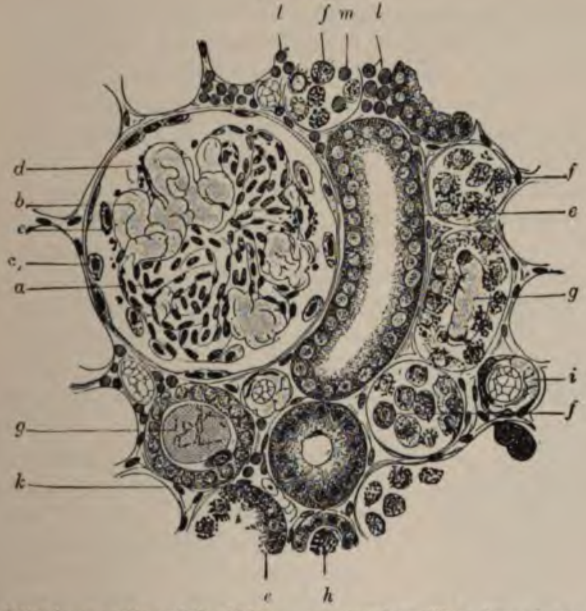
Amyloid Degeneration of the Kidneys.

Microscopically, the degeneration is first observed in the Malpighian bodies (Fig. 30). At first only a few of the capillary loops in each tuft are affected, but all the loops gradually become involved. The whole coil then presents an ill-defined outline and glistening surface. The change extends to the afferent arteries, to the capillary network around the tubules, to the arteriolæ rectæ of the medulla, and, in

advanced cases, to the intertubular tissue and to the tunica propria of the tubules. It is doubtful if the epithelium ever undergoes amyloid degeneration. The distribution of the change throughout the kidney may be very irregular.

At first, the tubes and epithelium appear normal. Many of the former contain the pale hyaline casts which appear in the urine. These are probably simple exudation-products, but they occasionally stain brown with iodine, and have been supposed to consist of amyloid.

FIG. 30.



Amyloid and fatty degeneration of the kidney. *a*, normal capillary loop; *b*, amyloid capillary loop; *c*, fatty epithelium of the glomerulus; *c,,* fatty epithelium of the capsule; *d*, oil-drops on the capillary walls; *e*, fatty epithelial cells *in situ*; *f*, loosened fatty epithelial cells; *g*, hyaline coagula (forming "casts"); *h*, fatty cast in section; *i*, amyloid artery; *k*, amyloid capillary; *l*, infiltration of connective tissue with leucocytes; *m*, round-cells (leucocytes) inside a uriniferous tubule. × 300. (Ziegler.)

According to Ziegler, however, these casts do not exhibit the other typical reactions of amyloid. As the change advances the diminished blood-supply and the direct pressure of the new material may lead to atrophy and fatty degeneration of both glomerular and tubular epithelium; but more frequently these changes occur at an earlier stage, and are due to chronic parenchymatous nephritis. The tubes, in such cases, are distended with both cloudy and fatty cells, and the intertubular tissue is more or less infiltrated with round cells (*large white amyloid kidney*). In the later stages of the process there is almost always increase of the intertubular tissue, which, together with the disappearance of tubes, leads to shrinking and toughening of the organ, to adhesion of the capsule, to irregularity of the surface, and to formation of small retention cysts.

The *naked-eye* appearances vary with the extent of the degeneration, and may be modified by the presence of chronic nephritis.

If thin slices of a kidney in the earliest stages of amyloid degeneration be stained with iodine, a Malpighian body will here and there appear as a brown dot, and the straight arteries of the pyramids as brown lines, although the unstained kidney is still normal in appearance. As the disease advances, the organ enlarges, especially the cortex. The surface is smooth, and the capsule separates readily. The enlarged cortex is remarkably pale and anæmic, and has a peculiar translucent, homogeneous, wax-like appearance. Its consistence is hard and firm. A few scattered vessels may be seen on the surface, and the bases of the pyramids sometimes exhibit increased vascularity. If iodine be applied to the cut surface (p. 67), the Malpighian bodies and the arteries of the cortex become mapped out as clearly as in an artificial injection (Fig. 31). The enlarged Malpighian bodies may, indeed, be seen as glistening semi-translucent points before the iodine is applied. Frequently, the homogeneous appearance of the cortex is interrupted by minute, opaque, yellowish-white lines and markings: these are produced by fatty changes in the epithelium of the tubes, due generally to concomitant nephritis. Ultimately the capsule becomes more or less adherent, and slight irregular depressions make their appearance upon the surface of the organ; the latter are due to atrophic changes in some of the tubes. If, as is usually the case, the process is associated with an increase in the intertubular connective tissue, the atrophy may render the organ even smaller than normal.

Fig. 31.

Amyloid kidney. Stained with iodine. The dark parts represent the Malpighian bodies and arteries which have undergone the amyloid change. From a child. Natural size

Sometimes the enlargement of the organs is very great. In these cases the increase in size is mainly due to inflammatory changes, such as have been referred to. The frequency with which such combinations occur renders it advisable to examine all large pale kidneys for amyloid changes.

Effects.—The capillary walls in the Malpighian bodies are so altered that albumin and an increased quantity of fluid readily permeate them; and thus is produced the large amount of urine, sometimes loaded with albumin, which characterizes the earlier stages of this affection; the polyuria is, however, not so great as in the granular contracted kidney, in which disease the general arterial tension is raised. If inflammatory changes supervene, the urine diminishes in quantity. The excretion of urea is less interfered with than in any form of nephritis, nor is the internal secretion seriously affected, for uræmia seldom occurs in uncomplicated cases. Tube-casts are rarely

numerous; they are for the most part hyaline or finely granular, though sometimes they are covered with fatty epithelium. In advanced cases there is marked dropsy.

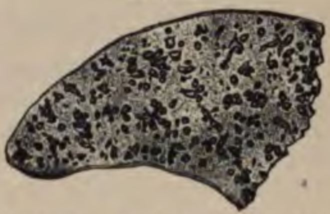
The association of chronic tubal nephritis with amyloid change is so frequent as to suggest the possibility of a common cause to the two conditions.

Amyloid Degeneration of the Spleen.

Two forms are generally described:—(1) the **sago** spleen, the commoner form, in which the disease commences in the Malpighian follicles; and (2) the **diffuse** form, in which the whole splenic pulp is first implicated, and in which the Malpighian follicles often escape. The two forms are occasionally combined.

In the **sago** spleen the first *microscopical* changes are observed in the capillaries and arterioles of the Malpighian follicles. The reticulum, of which the follicle largely consists, is next involved, then the small vessels in the neighborhood, and finally the pulp. In the early stages, the central artery of the corpuscle usually escapes. When it becomes affected, the change is first observed in its middle coat. In the **diffuse** form the degeneration begins in the neighborhood of the capillary veins of the pulp, and spreads thence to the trabeculæ, arterial capillaries, and possibly—though this is very doubtful—to the cells. The Malpighian follicles often escape, but their central arteries are generally involved.

FIG. 32.



Amyloid sago spleen. Stained with iodine. The Malpighian follicles are darkly stained, and as a rule have unstained centres. From a child. Natural size.

To the *naked eye*, the **sago** spleen is more or less enlarged; its weight and density are also increased. The cut surface is smooth, dry, and studded all over with small, glistening, sago-like bodies, varying in size from a millet to a hemp seed. These are stained reddish-brown by the iodine solution; but, as the central artery generally escapes, the mahogany-colored nodules have pale centres. These nodules may enlarge until they occupy a considerable portion of the organ, although in earlier stages of the affection they are so minute that they can be seen only in thin sections of the tissue. In the later stages, therefore, there is a considerable resemblance between iodine-stained sections of liver and of spleen, as may be seen by comparing Figs. 29 and 32.

In the **diffuse form** the organ often attains a much larger size than is met with in the sago spleen. It is remarkably hard and firm, and the capsule is tense and transparent. On section, it presents a dry, homogeneous, translucent, bloodless surface; it is in some cases pale, in others of a mottled reddish-brown color. Thin sections can be readily made with a knife, the organ cutting like soft wax. The cor-

puscles, if affected, are not visible, as in the former variety, being obscured by the surrounding pulp.

Amyloid Degeneration of the Alimentary Canal.

The mucous, submucous, and muscular coats of the œsophagus, stomach, and intestines may be involved; but these organs are probably never affected alone. The change frequently coexists with tubercular ulceration. In the alimentary tract the disease is very apt to escape observation, as it usually produces but little alteration in the appearance of the parts. The mucous membrane may be pale, smooth, translucent, and œdematous; in very advanced cases there may be some rigidity and thickening of the bowel-wall, and even ulcers—due, it has been suggested, to the snapping off of rigid villi. The effect of the application of iodine to the washed mucous surface is very characteristic. In the small intestine—perhaps the part most commonly affected—small, closely set, reddish-brown points appear over the whole surface of the membrane; these correspond to the intestinal villi, the arteries and capillaries of which have undergone the amyloid change. In the stomach and œsophagus the vessels may be similarly mapped out by iodine (p. 67).

The change in the intestine gives rise to serous diarrhœa, probably due to increased permeability of the degenerated vessel-walls. Both absorption and secretion are much impaired, so that implication of the alimentary tract has a grave general effect.

Corpora Amylacea.

Corpora amylacea, or "amyloid bodies," were formerly looked upon as consisting of amyloid substance; there appears, however, with the exception of a certain similarity in their behavior with iodine and sulphuric acid, to be no connection between them. They are said to consist largely of lecithin.

They are round or oval bodies, formed of a succession of concentric layers, and are often changed to a deep blue color by iodine, thus bearing, both in structure and chemical properties, a strong resemblance to granules of vegetable starch (Fig. 33); but, sometimes, the blue is exhibited only after the subsequent addition of sulphuric acid, and thus a resemblance is shown to amyloid substance. Many of these bodies, however, are colored green, or even brown, by these reagents. The green is due to their admixture with nitrogenous matters, which give a yellow color with iodine, and hence the combination yields a green. The greater the amount of nitrogenous matter the browner does the color become. They vary in size from microscopic granules to bodies which are distinctly visible to the naked eye, sometimes being as much as a sixth of an inch in diameter. The larger are usually formed by the

FIG. 33.

Corpora amylacea from the prostate. (Virchow.)

conglomeration of smaller granules, which are often enclosed by a common envelope.

They especially occur in conditions of atrophy or softening of the nervous system. The ependyma of the ventricles, the white substance of the brain, the choroid plexus, the optic nerve and retina, and the spinal cord are their favorite seats. The larger forms are met with most frequently in the prostate. The prostate of nearly every adult contains some of these bodies; and they may accumulate in that organ to such an extent as to form large concretions. They are occasionally met with in the lungs, and in mucous and serous membranes.

The corpora amylacea, especially those occurring in the choriod plexus and in the lateral ventricles, are very liable to become calcified, and they then constitute one form of "brain sand" which is so often met with in these situations.

The nature of these bodies is unknown: from their laminated structure they would appear to be formed by gradual deposition upon a central nucleus; but in the prostate they are probably produced by degeneration of the glandular cells.

CALCAREOUS INFILTRATION.

Calcareous Infiltration or *Calcification* consists in the *infiltration* of tissues with calcareous particles. It is a purely *passive* process, the cells taking no part in it: the tissue is gradually petrified by the deposit of earthy salts from the blood. It is difficult to find a physiological type, but perhaps the deposit of earthy salts in the walls of the primary areolæ (see Rickets) in a growing bone may be regarded as such. *Ossification* is quite distinct from *calcification*, for in the latter everything points to life and growth; the cells are undergoing *active* changes, and are obviously concerned in receiving the salts from the lymph and in combining them most intimately with the organic matrix.

Etiology.—Earthy salts in solution, chiefly the *phosphates* and *carbonates of calcium and magnesium*, are brought to the part by blood and lymph, carbon dioxide being probably the solvent. In inquiring why these salts should be permanently deposited in certain tissues, attention must be directed to the facts that, in the immense majority of cases, the tissues affected are dead or dying, and that calcification is a common senile change. It is probable, therefore, that feeble nutritive activity and a retarded blood-stream are together responsible for its occurrence. Rindfleisch taught that carbon dioxide escaped from the stagnating lymph-stream, and that the earthy salts were consequently precipitated: more recently, others have held that calcification is due to a combination of these salts with certain albuminoid bodies and with fatty acids. Some authors attribute the calcification of arteries met with in old age to deficiency of sodium chloride in the blood and tissues, this defect permitting the deposition of calcium salts.

Sometimes calcareous infiltration appears to be due to an absolute in-

crease of calcareous salts in the blood, such as may be supposed to occur in extensive caries and in osteomalacia. A portion of the excess is then deposited more or less widely in the tissues—especially in the lymphatic glands and kidneys, and less frequently in the lungs, stomach, intestines, dura mater, and liver. The deposit takes place chiefly in the connective tissue and least active constituent of the organ, which, moreover, immediately surrounds the vessels—*e. g.*, in the interlobular tissue of the lungs and in the stroma between the glands of the stomach; but, in the kidney, the epithelium is infiltrated as well as the intertubular tissue. Analogous to this form of calcification is the deposition of the biurate of sodium which takes place, especially in cartilage, fibrous tissue, and synovial membranes, and forms the commonest manifestation of gout. It is probable that, in this case also, the deposit occurs first in tissues in which the nutritive activity is most feeble. A certain amount of chalky—like fatty—infiltration may perhaps occur without marked impairment of function; but, as completely calcified parts are certainly dead, either the infiltration has the power to kill or it affects dying parts.

Seats.—As a senile change, calcification affects most frequently the arteries and hyaline cartilages—excepting articular cartilages. It occurs similarly in pathological tissues of which the life is feeble—*e. g.*, in uterine myomata after the climacteric and in old scars. Dead tissues locked up in the body are also very likely to become calcified—*e. g.*, thrombi (*phleboliths*), parasites (Fig. 34), atheromatous patches in arteries, and the caseous masses so common in lungs and lymphatic glands which have undergone chronic tubercular changes. The best example is the complete calcification of a dead fœtus, which sometimes occurs when this is retained in the abdomen, in the case of an extra-uterine fœtation (*lithopædion*).

Fig. 34.

Calcified trichinæ in muscle. In two of the parasites the capsules and contents are so far calcified that hardly any trace of the coiled embryo remains. In the other the trichina is dead, shrivelled and becoming infiltrated. × 30.

Appearances.—1. **Microscopic.**—The calcareous particles make their appearance both within the cells and in the intercellular substance; they are much more frequent, however, in the latter situation. They are seen at first as very fine dust scattered irregularly through the intercellular substance (Fig. 35). They are characterized, when viewed by transmitted light, by their opacity, black color, irregular outline, and solubility in dilute mineral acids, usually with evolution of bubbles of carbon dioxide. They gradually increase in number until ultimately large tracts of tissue may be converted into an opaque calcareous mass, in which the cells are enclosed and can no longer be recognized. These large masses have a sharp black irregular outline,

and, as the calcification becomes complete, acquires a homogeneous, glistening, semi-transparent appearance. The cells themselves are much less frequently infiltrated, being merely enclosed and obscured by the calcified intercellular substance. Calcareous particles may, however, make their appearance in the protoplasm, and, gradually increasing,

FIG. 35.

A calcifying sarcoma. From a secondary tumor of the lung. Showing the calcification of a spindle-celled growth. × 200.

convert the cell into a homogeneous calcareous body. Calcification of ganglion-cells alone is not uncommon in degenerative processes in the brain.

If the saline matters are dissolved out with a little dilute mineral acid, the structure of the part may be again recognized, unless, indeed —as is so often the case—it has been destroyed by some antecedent change.

2. Naked Eye.—Apart from the microscope, calcification can be recognized more readily by touch than by sight. If the calcareous particles cohere in minute groups, as is common when the process succeeds that of caseation, a white mortar-like substance is produced. When the cohesion is more marked, the deposit is comparable to fine sand; and all stages between this and solid stony masses may be met with. The latter break with an irregular surface and present a yellowish or grayish aspect. A calcified part is dead and inert: it undergoes no further change.

Effects.—Calcification must be looked upon in many cases as a salutary process, the impregnation with calcareous matter preventing subsequent changes in the part. This is especially the case when it occurs in caseous *tubercular foci*, as it imprisons the cause of the disease. It is doubtful whether calcification of a *tumor* is of any benefit to the patient, for the infiltration is probably limited to the dead or dying parts, and does not hinder the spread of the actively growing portions. On the other hand, when it affects the arterial system, calcification may be attended with the most deleterious consequences, as will be seen in the following section.

Concretions of various kinds may be found in the gall-bladder, bile-ducts, pelves of the kidneys, ureters, urinary bladder, and other parts. They are commonly preceded by catarrh of the living membrane of the duct in which they are situated, due to bacterial infection. They will be referred to when diseases of the affected organs are discussed.

Calcification of Arteries.

Calcified plates are frequently met with in the intima of the aorta and other large arteries as part of the change known as *atheroma*.

Sometimes a more or less general calcification occurs, especially as a senile change, and is then frequently associated with other degenerative changes in the arterial walls. It is commonest in vessels of medium size, the arteries of the upper and lower extremities and of the brain being frequently affected. It may affect both internal and middle coats, often commencing in the muscle-cells of the latter. The calcareous particles, deposited from the vasa vasorum, make their appearance at first around and within the nucleus, and gradually accumulate until they fill the cell, which becomes converted into a small calcareous flake. The process may go on until the muscular coat is completely calcified; or it may be limited to isolated portions of the coat, giving rise to numerous irregularly distributed calcareous rings and plates, somewhat suggestive of a piece of ipecacuanha root. These are best seen in vessels clarified and dried. From the muscular it may extend to the external and internal coats, until ultimately the vessel becomes calcified throughout.

The vessel thus calcified loses its elasticity and contractility; its lumen is diminished, and it is transformed into a hard, rigid, brittle tube, or "pipe-stem artery" (Fig. 36). Such an artery is partially protected against dilatation, but is predisposed to rupture: in amputations great difficulty may be found in securing such vessels, as ligatures cut through them at once. The nutrition of parts supplied by them is more or less impaired, and general calcification of the arteries of the lower limb therefore predisposes to *senile gangrene* (p. 35), inas-

FIG. 36.

Femoral artery, showing extensive senile calcification, the whole vessel consisting of a mass of calcareous plates. Natural size.

much as it renders the vessels less able to adapt themselves to the varying requirements of the circulation.

PIGMENTARY CHANGES.

Pathological pigmentation is a term used to imply the abnormal appearance of some kind of pigment in the tissues, and includes many conditions differing widely in their nature and origin.

The pigment may be derived: (1) directly from *hæmoglobin;* (2) from the blood by *cell-action;* (3) from *bile;* (4) from *extraneous substances* introduced into the body.

1. **Hæmatogenous pigments,** derived directly from hæmoglobin, are the commonest. Red corpuscles break up and their coloring-matter is set free. This occurs occasionally within the vessels, as in malaria and septicæmia, but more frequently after escape of the corpuscles into the tissues. The latter is due either to wounds or rupture of the vessels, or to congestion or inflammation without any visible breach in the vessel-wall. Such instances of pigmentation are common; among them may be mentioned bruises of the skin, small hemorrhages in the neighborhood of varicose veins and passively congested parts, and stains after syphilitic and other inflammatory lesions.

The two principal pigments which form the final products of the breaking up of red corpuscles in the tissues are *hæmosiderin* and *hæmatoidin.*

Hæmosiderin[1]—an iron-containing pigment—probably formed by the action of living cells, gives the ordinary reactions of iron and is found in the liver, spleen, and other organs whenever excessive destruction of blood-corpuscles (*hæmolysis*) is present. It is also found mixed with hæmatoidin, which it closely resembles in appearance.

Hæmatoidin—an iron-free pigment—is probably identical with bilirubin, which is also a derivative of hæmoglobin. It exhibits similar reactions when treated with concentrated mineral acids, displaying the same variations of green, blue, rose, and yellow colors. It is insoluble in water, alcohol, ether, acetic acid, and in dilute mineral acids and alkalies; it is soluble in concentrated acids and in the caustic alkalies, giving, in the latter case, a red color.

These final stages of extravasated blood occur in two forms—*granular* and *crystalline.* Both are of a very permanent nature, and may remain unaltered for years.

The *granules* of hæmatoidin vary in size from the smallest particles to masses as large as a red blood-corpuscle. The larger are commonly irregular in shape, sharply defined, and more or less glistening. Their color varies from yellowish-red to brown or black; the older they are the darker they become. The smaller granules are usually dull and opaque.

The *crystals* of hæmatoidin are opaque rhombic prisms, usually of a yellowish-red or ruby-red color, sometimes approaching to brown or black. They may also occur as little plates and fine needles, but these are less common forms (Fig. 37). They are in most cases so small that considerable care is required to recognize their crystalline nature

[1] Greek *αἷμα*, blood; *σίδηρος*, iron.

under the microscope, and they may easily be overlooked as merely irregular granular masses. In some cases, however, they attain a larger size.

Fig. 37.

Hæmatoidin crystals.

Whether hæmoglobin is converted into granular or crystalline hæmatoidin appears to depend partly upon the tissue in which it is situated, and partly upon the amount of extravasation. Crystals are exceedingly common in some situations—*e. g.*, the brain and ovaries; whereas in others—*e. g.*, mucous membranes—only granules are met with.

According to Kunkel, some of the pigment left by hæmoglobin is pure hydrated peroxide of iron.

The changes in color which occur after a bruise—first purple, then green, and finally yellow—are due to corresponding changes in the extravasated blood. (1) Some of the fluid and cells are absorbed at once by the lymphatics, while the hæmoglobin is dissolved out of many of the red corpuscles, and the stromata disappear—no doubt after fatty degeneration. Thus there is formed a red fluid which infiltrates the tissues, and stains them yellow or brownish red—the cells being colored more deeply than the intercellular substance, or than the membranous or fibrous structures. The color changes on the surface are due to alterations in this dissolved hæmoglobin, which is soon decomposed into hæmatin or hæmochromogen and an albuminous body. Part of the coloring-matter is reabsorbed and appears in the urine as urobilin; the rest undergoes a change and is finally deposited as hæmosiderin or hæmatoidin. (2) Many corpuscles simply shrivel into brownish granular masses of pigment—said to occur chiefly in "hæmatomata," or tumor-like collections of blood. (3) Other red corpuscles, or the pigment-masses resulting from them, are taken up by leucocytes, which are attracted in large numbers into the extravasation. The pigment thus taken up may be deposited in the neighborhood, or may be carried by the surviving leucocytes into the lymphatics, when it will probably be arrested in the nearest lymphatic glands, the lymph-paths being thus marked out by pigment; or it may pass through into the circulation and give rise to pigment-emboli of various organs.

The *ultimate fate* of extravasations is by no means uniform.

(1) Absorption may be, and in vascular parts often is, to the naked eye, complete; but even then crystals or granules of pigment may not infrequently be found by the aid of the microscope. (2) A scar—yellowish, brownish, or blackish, from granular or crystalline pigment—may mark the site of the destruction of tissue by hemorrhage. (3) A collection of chocolate-colored fluid may long remain surrounded by a capsule of inflammatory tissue, often lined by layers of clot, more or less decolorized and organized (*hæmatoma*): the fluid contains pigment and fat-granules along with cholesterin-crystals. (4) A cavity, with more or less pigmented walls, containing clear fluid may be left—especially in the brain. (5) The fluid may be absorbed, and the clot become completely decolorized and organized—a good example of

which is seen in the so-called "membranous pachymeningitis." The process can frequently be watched in aseptic wounds.

Hæmatogenous pigmentation is a very common occurrence, though one of little importance. The presence of pigment in or between the cells of a tissue can have little effect on the elements or their functions: any disturbance of these must be attributed rather to the conditions upon which the formation of the pigment depends.

The presence of this form of pigmentation may be the only evidence of antecedent disease, such as cerebral hemorrhage, in which yellow staining may be left; or chronic catarrh of mucous membranes, in which slate-colored pigmentation marks the site of the inflammation. The pigmentation of the liver and spleen in malaria, and of the liver and other organs in the condition known as hæmochromatosis (*bronzed diabetes*), is of similar nature.

2. Pigment Derived from the Blood by Cell-action.—The chief examples of this change are melanotic warts, nævi, sarcomata, carcinomata, and Addison's disease. The pigment lies in the cells more often than between them, is granular, and varies from yellow to black in color: it contains sulphur but not iron. It differs spectroscopically from all known blood-pigments, and is one of the melanins. Pigmented growths generally arise from pigmented tissues (Fig. 38). (See Melanotic Sarcoma, p. 123.)

The cause of the pigmentation of the skin in *Addison's disease* is not satisfactorily explained. Irritation of the abdominal sympathetic is believed to cause increased pigmentation, as in some cases of abdominal tumor, but of this there is no certain proof. The pigmentation in Addison's disease is merely an exaggeration of the normal, but it is most marked at points of pressure (irritation). It has been suggested that the suprarenal glands normally eliminate waste products derived from breaking-up of hæmoglobin. On the other hand they apparently contain a "chromogen," or substance capable of being converted into pigment. Variations in the normal pigmentation of the skin occur during pregnancy and in various uterine troubles, as well as in melanoderma; but no certain explanation of these, or of blanching of the hair from neuralgia or fright, can be offered.

FIG. 38.

Cells containing pigment. From a melanotic sarcoma of the liver. × 350.

3. Pigmentation from Bile.—This form of pigmentation is known as **jaundice** (*icterus*), and is due to obstruction of the bile-passages. The obstruction may occur in the small ducts, in the hepatic duct, or in the common bile-duct. It is most frequently due to swelling of the walls from catarrhal inflammation, to blocking of the lumen by gall-stones, or to the pressure of a new growth outside the duct. The continued secretion of the bile behind the obstruction causes a rise in the pressure within the smaller ducts, with consequent absorption of bile by the veins and lymphatics and its subsequent distribution throughout the

body. It is first perceptible in the urine, soon after in the conjunctivæ and skin, and may ultimately stain all the tissues yellow or greenish yellow. The staining of the skin persists some time after the bile has ceased to circulate in the blood. When the seat of obstruction is in the small bile-ducts, as in cirrhosis, the staining may be limited to small areas of the liver.

The pigmentation is due to diffuse staining; but granules and even crystals of bilirubin are occasionally found, especially in *icterus neonatorum*.

With regard to the slight jaundice that occurs in septicæmia, the malignant forms of acute infective fevers, and some other diseases (*toxic jaundice*), no marked obstruction can be demonstrated in the ducts, and the exact cause is doubtful. It is probable that increased consistence of the bile, and diminished pressure in the bloodvessels, combined with catarrh of the smaller bile-ducts, cause the tension in the ducts to exceed that in the bloodvessels, or at any rate in the lymphatics, and thus induce a slight absorption of bile into the vessels and a consequent mild degree of obstructive jaundice. It has also been suggested that the hepatic cells may in certain cases, by some perversion of function, discharge the bile into the lymphatics surrounding them, instead of into the bile-ducts.

4. **Pigmentation by Extraneous Substances.**—Examples of this form of pigmentation occur in the lungs, the skin, the lymphatic glands, and the mucous membranes. The substances accredited with its production are carbon, silver, lead, arsenic, and such pigments as may be used artificially; to these may be added, in rare instances, mercury and picric acid.

The inhalation of fine particles of **carbon** and other substances produces pigmentation of the lungs and bronchial glands. This is of considerable importance and will be described in detail later on. (See Pneumoconiosis.)

The prolonged administration of salts of **silver** leads to the development in the skin and adjacent mucous membranes of a peculiar brownish-gray color. That portion of the metal which finds its way to these parts is, owing most probably to the action of light, deposited as minute particles of reduced silver. This condition is known as *argyriasis:* it is permanent.

The existence of **lead** in the tissues is often demonstrated by the presence of a thin, black, well-defined line *in* the gums where they are in contact with the teeth. It is due to the action of the sulphuretted hydrogen, given off by the decomposing matter which collects between the mucous membrane and the teeth, upon the lead in the adjacent tissue. The "lead-line" is, therefore, usually broken, and often absent in those whose teeth are kept thoroughly clean, even though other symptoms of lead-poisoning may be present. Pigmentation of the mucous membrane of the large intestine has been found associated with the presence of considerable quantities of lead and of **mercury** respectively in that part of the alimentary tract.

In **tattooing**, artificial pigments are placed in the deeper layers of the skin. Most of the pigment remains in its original position. Of the remainder, some is removed by the phagocytic leucocytes, and some is washed on into the lymphatics and filtered out by the glands, where it is retained.

Dead tissues in process of separation are frequently discolored—black, greenish black, or slate-gray—by the action of sulphuretted hydrogen upon the decomposed hæmoglobin (p. 37); and *atrophied organs*, in which the pigment is, as it were, concentrated, often appear darker than normal. Neither of these, however, is an instance of true pigmentation.

Metaplasia.

The present may be a convenient place at which to allude to the change which epithelial cells at times undergo as the result of alteration in their surrounding conditions, although it is not strictly a degeneration. Thus columnar epithelium may be converted into squamous or into flattened pavement epithelium. An instance of the former may be seen in cases in which the uterus is inverted and prolapsed: the lining mucous membrane is thus exposed to the outer air and to irritation from contact with clothes, and under these conditions the columnar cells become squamous in type. The columnar cells lining ovarian and other cysts may, on the other hand, become flattened and thinned as the cysts enlarge, this alteration being produced by lateral stretching combined with direct pressure from the cyst-contents. An opposite change occurs in villous growths in the bladder, which often exhibit a columnar covering in place of the transitional epithelium from which they arise. The ciliated epithelial cells lining the nasal cavities become squamous in type as a result of infective or traumatic inflammation (ozæna, cautery). Change of type of the above nature is called *metaplasia*. It is often seen in the secondary growths arising from carcinomata.

CHAPTER IV.

HYPERTROPHY.

THE morbid processes thus far described have been attended either by arrest or by impairment of nutrition; there remain to be considered those in which the nutrition is so changed that formation exceeds waste, and increase of tissue results. They include hypertrophy and repair, and tumor-formation. Repair of tissue will be considered in Chapter VI. as part of the reaction of the body to irritants.

Hypertrophy may be defined as "*an increase in the size, weight, and functional activity of a part beyond the limit of health, due to an orderly enlargement or multiplication of all its normal constituents.*" From this definition it will be seen that the *nature* of the process is strictly physiological; in *extent* only it is pathological. External form and minute structure alike exhibit a single change—that of size. The weight of a hypertrophied organ, however, gives the most reliable indication of the extent of the change. Strictly proportional to the increase in size and weight is that in work done.

The terms "false hypertrophy" and "pseudohypertrophy" are used to indicate that the increase in size, while presenting a superficial resemblance to hypertrophy, is due either to the unequal overgrowth of the tissue-elements, or to the growth of only one of them—often at the expense of the rest; and that there is no increase in work done. Thus *pseudohypertrophic muscular paralysis* is characterized by a marked enlargement of certain muscles, due to an increase in their connective-tissue elements, accompanied by atrophy of the muscular tissue and diminished capacity for work.

Hypertrophy is said to be "simple" when due to an increase in the size of the tissue-elements of the affected part; "numerical," when due to an increase in their number. The latter is also called *hyperplasia*. These terms are of little practical value; for hypertrophy is in nearly all cases believed to be numerical; and in most cases it is simple as well. In the great example of physiological hypertrophy—the gravid uterus—some of the muscular fibres may be ten times their normal size.

Etiology.—The principal factors in the production of hypertrophy appear to be (1) *increased functional activity*, and (2) *excessive nutritive supply*. Other agents to which more or less importance is attached are (3) *diminished waste*; (4) *removal of resistances to growth* offered by neighboring or controlling tissues (*altered tissue-tension*; (5) *congenital conditions*, such as an increase in the embryonic rudiment or an excessive vital energy.

1. In a large number of cases hypertrophy seems to occur as a re-

sponse *to a demand which has arisen for* **increased work.** An example of this occurs when a difficulty arises in the circulation. The difficulty may be due to a narrowing in the arterioles, to obstruction at one of the orifices of the heart, or to some interference with the movements of the heart-walls themselves, such as may be caused by the permanent adhesion of the visceral and parietal surfaces of the pericardium. Under the altered conditions the normal blood-flow can only be maintained by increased work on the part of the heart. In such circumstances it generally happens that in proportion as the difficulty gradually makes itself felt, so the part or parts of the heart, upon which the extra work required falls, gradually hypertrophy : thus the increased demand is permanently provided for. At the same time the supply of blood through the coronary arteries is also increased. It would seem, indeed, that this is the connecting link between the increased work and the production of the hypertrophy ; for if, through disease of the coronary arteries or other cause, the increase in the supply of blood to the heart cannot be effected, the requisite hypertrophy does not occur. When hypertrophy arises in this way it is termed *compensatory.*

In some instances a further explanation of the compensatory hypertrophy of the muscular walls of the heart seems possible. Regurgitation through the mitral orifice causes over-distention of the left auricle and stretching of its muscular walls, as well as overfulness of the supplying pulmonary vessels. The walls of the auricle, being in the position of an overweighted muscle, will subsequently contract with proportionately increased vigor, and, if the increased work is accompanied by a proportionately increased blood-supply, will gradually hypertrophy. The increased amount of blood consequently discharged into the left ventricle, just before its contraction, will distend the latter cavity and stretch the muscular fibres in its walls during the period of their relaxation, and will lead, therefore, in a similar way to hypertrophy of the left ventricle. The right ventricle will also undergo hypertrophy, due to the increased work done in forcing the blood through the lungs into the left side of the heart.

The power of the heart thus to hypertrophy is by no means unlimited. One source of limitation is very clear : this is in the blood-supply. If in any way the quality of the blood deteriorates, or the coronary vessels become rigid or partly obstructed, not only is increased growth an impossibility, but, as has already been said, fatty degeneration will inevitably ensue (p. 51). The other chief source of limitation lies in the "growing capacity" of the cells. When the original disease is of a progressive character, or when its ravages are increased by the help of allied diseases, it is clear that there must come a time when, even though the coronary circulation be apparently adequate, the inherited capabilities of the cells will fail, and growth consequently cease. Little is known concerning this inherited growing capacity, but it is a very important factor. Probably no increase of the blood-supply could save a thymus gland from atrophy or increase the number of adult ganglion-cells.

When muscle contracts frequently against a moderately increased load, it also hypertrophies, as is seen in training. Frequent contraction alone is insufficient, for the muscles of hands used actively, but not forcibly, do not enlarge, nor is frequent micturition in pyelitis followed by thickening of the muscular walls of the bladder. If, however, an obstruction occurs in the urinary passages, which the bladder can overcome by more powerful contraction, hypertrophy begins. Other examples of such *compensatory* hypertrophy may be seen in the walls of the intestine just above a permanent but not impermeable stricture, or in those of a vein in aneurismal varix, or of any bloodvessel through which an abnormal quantity of blood is forced.

When any organ is removed, or prevented from fulfilling its ordinary function, other organs, which take on its work, hypertrophy, receiving the blood which should have supplied the diseased organ as well as their own. This is best seen in the kidney; rarely in the testis and, perhaps, occasionally in the lung. The power of hypertrophy possessed by a glandular organ is only complete in fœtal life. If one kidney be destroyed before birth, the other will grow until it reaches double its normal weight, but if the damage occur later, the increase in the surviving organ will not exceed one-third of the original, and the reserve power of the organ will accordingly be less. Removal of one submaxillary gland is not necessarily followed by hypertrophy of other salivary glands; this occurs from more frequent stimulation of their secretory nerves, which probably produces the large submaxillary glands seen in epithelioma of the tongue. The kidneys, however, are under nerve-control in a different way; they seem to be excited to secrete by the presence in the blood of material suitable for their secretion, and hypertrophy naturally results from a continued and marked increase in the supply of blood containing such material—presumably the products of tissue-metabolism. Enlargement of lymphatic glands has been noted after removal of the spleen. Increased weight thrown on a bone causes thickening of it—*e. g.*, of the fibula in ununited fracture of the tibia.

2. **Increased nutritive supply** has already been considered in part. Attention must, however, be drawn to those cases in which *continued hyperæmia* from hard use and slight injuries is followed by thickening of the epithelium, as in a laborer's hand. Under similar conditions, a corn may arise. Increased blood-supply to a limb may cause lengthening of a bone, if the epiphysis be ununited, as is seen in large ulcers, caries, necrosis, and other conditions: the soft parts increase secondarily. Excessive growth of hair occurs in the hyperæmic zone of a chronic ulcer of the leg. In all probability increased vascular supply cannot by itself give rise to hypertrophy of any but the least specialized tissues.

3. **Diminished waste** is not a common cause of hypertrophy. The sclerosis of bone produced by small doses of phosphorus, the increase in size and strength of animals treated with small doses of arsenic, and the invigorating effect of this drug upon Styrian mountaineers, may perhaps be explained by diminished waste.

An example often quoted is the subinvoluted uterus, the bulk of which is made up of hypertrophied muscle and connective tissue with thick-walled vessels, but it is doubtful whether chronic inflammation is not largely responsible in these cases. Uncut hair and nails, and, in the case of many animals, unopposed teeth, grow till their vessels supply only nutriment enough to maintain them in their finally attained condition. These are, however, doubtful examples of hypertrophy.

4. **The removal of resistances to growth** is difficult to ascertain. It is sometimes mentioned as a factor in the production of such deformities as "knock-knee" (*genu valgum*): here excessive pressure is thrown on the outer articular surfaces of the femur and tibia, whilst the weight borne by the inner surfaces is less than normal, and they, consequently, grow excessively. This explanation is, however, incompatible with the occurrence of atrophy of the tibia in ununited fractures of that bone. Many *scleroses* or hypertrophies of connective tissue follow upon atrophy of the essential elements of an organ: the natural resistance between the two tissues (*tissue-tension*) has been removed.

5. There remain certain cases in which the etiology is even more doubtful than in the above. These are (1) cases of *true giant-growth*—*e. g.*, hypertrophy of the whole body (*giants*), of half the body, of whole limbs, or of parts of limbs, as fingers and toes: such parts are, on dissection, normal, except in size. A peculiar disease, acromegaly, characterized by enlargement of the extremities and of some of the cranial bones, is supposed to be due to disease of the pituitary body: and some cases of giant-growth are said to be examples of this condition. (2) Cases of *false giant-growth* occur in which the connective tissue alone is increased, the part being often misshapen: lymphatics are often dilated, and the bloodvessels may be nævoid. Examples are met with especially in the lip (*macrocheilia*), tongue (*macroglossia*), and lower extremity: these changes are by some authorities classed as lymphangiomata (p. 105). Hypertrophy of connective tissues and surface-epithelium may result from an excessive, though slow and impure, supply of blood. In some of the above, which are congenital or appear soon after birth, there may be **excessive vital energy** or **too large a number of the cells** forming the rudiment of the part or tissue.

Nothing is known of the causation of the enormous, but rare, enlargement of the female breast which may occur at puberty. Senile hypertrophy of the prostate is variously attributed to chronic inflammation and to adenomatous overgrowth: recent investigations point to the former as the more probable explanation (Daniel).

CHAPTER V.

TUMORS.

THE term "tumor" is primarily a clinical one, and signifies a local swelling. Thus an enlarged palpable kidney is usually spoken of as a renal tumor, altogether apart from any belief regarding the actual nature of the enlargement. In pathology, however, the term *tumor* denotes certain *local growths of new tissue*, the nature of which is but imperfectly known. No satisfactory definition is, therefore, possible. Nevertheless, tumors possess certain common characters which serve to distinguish them from allied conditions. The chief of these distinguishing features are, (1) an unusual independence of growth; (2) a varied degree of similarity of structure to that of the part from which the growth springs; (3) an extreme tendency of the component tissue-elements to undergo degeneration; and (4) a complete absence of all function, or, in other words, the absolute uselessness of the mass of new tissue. These characters must be considered in detail.

1. Independence of Growth.—There are no known laws regulating the growth of a tumor. *The growth is at first quite local*, and is limited to the continuous extension of the primary focus in its immediate neighborhood. Subsequently, by means that will presently be described, some forms of new-growth possess the power of reproducing themselves in other parts (p. 91). Two other striking differences between the growth of ordinary tissues and that of tumors must be mentioned. Firstly, *the nutrition of a tumor is disproportionate to the nutrition of the tissues in its immediate neighborhood, and often to that of the body taken as a whole.* Thus, in the case of a fatty tumor in the subcutaneous tissue, the body may become thin and the subcutaneous fat disappear, while the fatty tumor wastes but little if at all. Moreover, malignant growths often enlarge rapidly, while all the other tissues are as quickly emaciating. Secondly, *the nutrition of a tumor is often disproportionate to the age of the individual* in whom it occurs. This is seen in the growth of cancers which arise and grow rapidly in old people, while the rest of the tissues are gradually undergoing atrophy.

2. Peculiarities of Structure.—In structure, tumors more or less resemble normal tissues in some stage of their growth—every morbid new-growth having its prototype among the normal tissues. The resemblance, however, is at best incomplete, the tissue-elements often differing in form, arrangement, or some other detail; and tumors are thus always more or less atypical in their structure. As a rule, the difference between the normal and the abnormal tissue is so great that by means of the naked eye alone one can tell roughly where the one begins and the other ends.

Certain special forms of multiplication of the cells of tumors have been described. Thus the nucleus in malignant growths may undergo peculiar phases of mitosis, dividing into three daughter-nuclei instead of into two; while the mitotic threads are reduced in number, owing to failure of the original chromatin-filaments to undergo the usual longitudinal division. This latter peculiarity resembles the behavior of the cells of reproductive organs. Some observers have claimed to find evidence of conjugation taking place between the cells of malignant tumors, but this statement demands much fuller proof than has yet been adduced.

FIG. 39.

Muscle near shoulder, from a case of sarcoma of the head of the humerus, showing passage of small round cells (probably sarcomatous) along the "lines of least resistance," as in diffuse inflammation. Where the cells are thickest the muscle-fibres are obscured or have disappeared. (Boyd.)

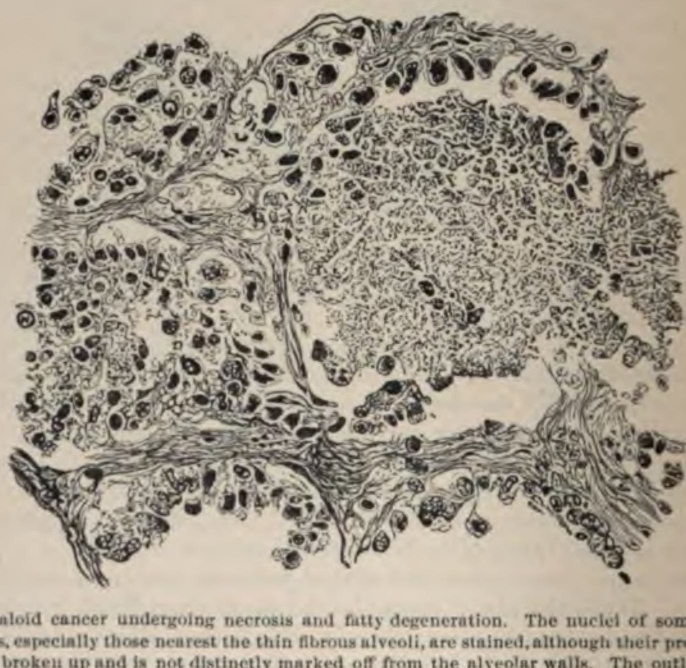
Tumors frequently originate in, and closely resemble, the connective tissues in their fully developed or embryonic state. Surface epithelium and gland-cells are also common sources of tumors, but are less closely copied by most of the new-growths arising from them. Voluntary muscles and nerve-cells may be invaded by new-growths, but do not often serve as starting-points. Tumors are generally supplied with bloodvessels and lymphatics, but not with nerves.

The terms *homologous* and *heterologous* are sometimes applied to tumors. When the tumor resembles the tissue from which it originates it is said to be homologous; when it differs from this it is said to be heterologous. A cartilaginous tumor arising from cartilage is, therefore, homologous, but occurring in any other than connective tissue, as, for example, in the parotid gland, is heterologous. The distinction is unimportant, for, in the example just given, the cartilage does not actually arise from the gland-cells of the parotid, but, in all probability, from the connective tissue or from a misplaced remnant of Meckel's cartilage. Heterologous tumors are generally secondary to some primary growth occurring in a distant part.

The relation of the tumor to the surrounding parts varies. Sometimes the tumor is *circumscribed,* merely displacing them and stretching and irritating their connective tissue, so that the latter comes to form a fibrous capsule around the tumor, which thus generally forms a spheroidal or lobulated mass. Lipomata, fibromata, and chondromata are usually thus encapsuled. In other cases the growth *invades* the adjacent structures. There is then no real line of demarcation between the tumor and the surrounding parts; and, although to the naked eye there may seem to be one, the microscope will show that the apparently healthy tissues are more or less infiltrated with cells from the parent growth (Fig. 39). In such a case, while the main body of the tumor may assume a roughly spheroidal shape, outlying discontinuous nodules may also be visible to the naked eye.

3. Retrogressive Changes.—A tumor very rarely disappears, thus differing from an inflammatory growth—*e. g.*, a gumma. It may either

FIG. 40.



Encephaloid cancer undergoing necrosis and fatty degeneration. The nuclei of some of the cells, especially those nearest the thin fibrous alveoli, are stained, although their protoplasm has broken up and is not distinctly marked off from the alveolar walls. The outlines of a few of the rest are still visible, though their contents are granular and their nuclei unstained. The greater number have been converted into a mass of granular fatty débris. × 250.

remain stationary or grow, slowly or rapidly. Sooner or later it usually becomes the seat of necrosis or degeneration. The time at which these commence varies. The more rapid the growth and the less specialized the new tissue, the less is its durability and the sooner do retrogressive changes occur. Many carcinomata and sarcomata develop

rapidly, and degenerate quickly (Fig. 40). They consist for the most part of cells: their elements are unstable and soon perish. Osseous tumors, on the other hand, develop slowly; they consist of a more highly organized tissue and have much greater stability.

The retrogressive changes are similar to those met with in the normal tissues. Thus, *fatty*, *pigmentary*, *calcareous*, *colloid*, and *mucoid degenerations* may occur. Tumors may also become the seats of *inflammation*, *ulceration*, *necrosis*, and *hemorrhage*.

4. Absence of Function.—No tumor serves any useful purpose. Some adenomata are said to have ducts and some secretory power, but these statements need further confirmation.

Recurrence and Generalization.—*A tumor may recur locally after removal; and, independently of removal, growths similar to the primary tumor may form* (1) *in the neighborhood of the parent growth*, (2) *in the nearest lymphatic glands, or* (3) *in more distant tissues or organs. Sometimes all these occur.* Each must be considered separately.

1. Reproduction in Adjacent Structures.—The recurrence of a tumor *in loco* after operative removal is due to some of its cells having been left behind, and is therefore much more likely to occur in those growths which infiltrate the surrounding tissues, and *really* extend beyond their *apparent* limits, than in those which are encapsuled. The cells left behind continue to grow and thus the tumor recurs. Apart from removal, cells may be carried to some little distance from the primary growth by lymph- or blood-currents, and, on becoming impacted, may form the nucleus of secondary nodules springing up around the original tumor. In some tumors local recurrence may take place many times, and lead to the death of the patient without any infection of glands or distant tissues.

2. Reproduction in the nearest Lymphatic Glands.—This is owing to the entry into the lymph-stream of cells from the primary growth. The cells are carried to the nearest lymphatic glands, and there are arrested, developing into secondary tumors of the same nature. When the lymphatic glands have themselves become the seat of secondary growths, they in their turn constitute new centres of infection, and may thus infect the more distant glands or the immediately adjacent tissues. When the lymph-sinuses of a gland are so blocked by new-growth that lymph cannot pass, a regurgitant flow is the natural result, and the lymph, bearing tumor-cells, has to find a new course and pass through other vessels and glands. In this way we can account for infection of the abdominal glands by a tumor of the lung, and for the numerous nodules in the skin which sometimes occur all around an atrophied scirrhus of the mamma. The tendency of new growths to reproduce themselves in the lymphatic glands varies very much. It is very marked in carcinomata, while in sarcomata it is comparatively slight. The reasons for these differences will be seen in subsequent chapters.

3. Reproduction in Distant Tissues.—This is usually the final stage

in the history of most malignant growths, and is known as their "generalization." The reproduction of the primary growth in distant tissues is, in the great majority of cases, owing to the entry of some of its elements into the lymph-stream; more rarely it may be effected through the bloodvessels. The secondary tumors are, therefore, the result of embolism of tumor-cells; and are of the same

FIG. 41.

Secondary growths of carcinoma in the liver. *a*, liver-tissue, congested; *b*, *b*, nodules of growth: *c*, *c'*, enlarged bloodvessels in and around nodules; *d*, highly vascular nodule of carcinoma, showing dark against the liver-tissue; *e*, *e*, umbilication of nodules when they reach the surface of the liver. × ⅔.

nature as the primary one, although they may be larger and are often softer, more vascular, and more active in growth. They may themselves become secondary centres of infection, and in the same way cause tertiary growths in parts beyond.

Although the general dissemination of a malignant growth is thus in most cases due to the transmission of its elements by the bloodstream, this is not the only way in which it may be brought about. Exceptional cases have been described in which the elements of a tumor have been distributed and have caused secondary growths in other ways, as by passing down the trachea, between the layers of the peritoneum, or from the kidneys down the ureters to the bladder.

Lastly, it must be borne in mind that growths may be secondary to each other only *in time*; that is, they may originate, independently of each other, from different primary foci.

We have spoken of generalization and lymphatic infection as being

due to the transference of tumor-cells from the primary growth. That the primary growth *is* the real source of the secondary growths is shown by their similarity in structure; by their time-relationship; by their demonstrable connection by means of blood- or lymph-channels; by the occasional discovery of tumor-cells impacted in the bloodvessels as emboli; by the invariable absence of secondary growths from non-vascular tissues such as cartilage and cornea; and by the occurrence of secondary growths in tissues in which primary tumors of the structure in question are never found.

Effects.—A tumor, by its growth, position, generalization and secondary changes, may, in many ways, produce marked effects on local and general nutrition: (1) The local growth may lead, mechanically, to the destruction of parts essential to life, as in the case of an otherwise innocent tumor in the pons or medulla; or it may similarly impair the action of important organs such as the lungs or stomach, and thus lessen the exchange of gases in the former or interfere with the digestive changes in, or passage of food through, the latter. (2) The rapidity and extent of the growth may lead to the abstraction of the nutriment needed for the maintenance of the normal tissues. (3) Hemorrhage may occur into or from a tumor and give rise to anæmia, as in the marked hæmaturia which characterizes growths in the kidney. (4) Inflammation, ulceration, and septic absorption may occur, as in epithelioma of the tongue. (5) Pain and anxiety may cause anorexia and sleeplessness. (6) Some abnormal and deleterious substances may be discharged into the blood-stream by the tumor-cells, although this is at present a purely hypothetical supposition. (7) Many of these effects may be increased by similar action on the part of secondary growths. In these ways tumors may lead to wasting, loss of strength, and anæmia; in other words, to the condition known as the *cachexia of malignant disease.*

Locally, a tumor acts as a foreign body, irritating the cells which come in contact with it at its periphery, and causing proliferation of the connective-tissue elements. A zone of small round cells of an "inflammatory" nature is therefore seen surrounding a rapidly growing tumor, and these may become organized into the fibrous capsule which usually surrounds benignant growths.

Clinical Course.—Tumors are divided clinically into two great types, the *simple* and the *malignant.*

A **simple** or **innocent tumor** is one which grows slowly and steadily, or, having attained a certain size, remains stationary. It consists of tissue closely resembling some normal adult tissue, and is generally surrounded by a distinct capsule out of which it can be completely shelled—for there is no infiltration of surrounding parts. Consequently, it seldom recurs locally after removal, and secondary growths in glands or elsewhere do not result from it. Its interference with health is only mechanical, unless some accident—as inflammation—

occur in it. Tumors of the fully developed connective-tissue type generally pursue this course, and may grow to a huge size.

A malignant tumor, on the other hand, grows rapidly and tends to enlarge continuously. It consists of tissue which is markedly atypical, and is, as a rule, unencapsuled, progressively infiltrating the surrounding tissues, and presenting no clear line of demarcation as a guide to removal. Complete removal is, therefore, very difficult, and subsequent recurrence, locally and in distant parts, probable. Though the patient is often in excellent health when the tumor first appears, its effects soon give rise to the cachexia just described. The more rapidly and the more completely a tumor produces these results, the greater is said to be its *malignancy*. Growths vary much in these respects, and a sharp dividing-line between innocent and malignant growths cannot always be drawn. Some unencapsuled growths are innocent (gliomata); some having the structure of malignant growths enlarge continuously, but do not invade glands or distant parts (rodent ulcer); while others recur in neighboring glands, but not in distant parts (epithelioma of tongue). Some growths, at first innocent, occasionally become malignant (papilloma, adenoma). Sarcomata and carcinomata furnish the best examples of malignant tumors.

Etiology.—Of the etiology of tumors, as a class, nothing certain is at present known. A few scattered facts have, however, been ascertained, throwing light on the causation of certain divisions of the group. Recent research has been devoted almost entirely to the study of the malignant tumors, especially carcinomata, while simple growths have been comparatively neglected. Little attempt has been made to treat the question from a general point of view.

It is, indeed, possible that it may be necessary in the light of additional knowledge, to subdivide the group, and to separate different varieties of tumor one from another, just as certain processes formerly looked upon as new-growths have now been removed from this class and recognized as inflammatory. Of such, tubercular and syphilitic granulomata afford instances. In the same way future analysis may carry the process further and resolve the present apparently homogeneous group of tumors into a variety of separate formations due to entirely different causes. At present, however, there is no sign of any probable line of cleavage. Tumors form a group characterized by well-defined peculiarities which differentiate them from other pathological conditions (p. 88); and, while they continue to form a class by themselves, it is necessary that any cause suggested to account for their production should apply to the whole group and not merely to isolated fractions of it.

The objection may, indeed, be here raised that the malignant growths do form a class apart, and that, therefore, for the members of this group, a method of causation different from that of other neoplasms is to be sought. Closer consideration, however, shows that at the present time there are no sufficient grounds for maintaining such a

distinction. The qualities which constitute malignancy differ in degree rather than in kind from the characteristics of benign growths, as has just been shown.

It seems clearly established that all tumors originate as *local lesions*, and are not, as has been suggested, manifestations of some general constitutional disease. *Heredity* appears to play some part in the causation of certain growths, especially those of the uterus and mamma, but it is difficult to estimate the exact weight that should be attached to this factor.

Various hypotheses have been propounded with respect to the etiology of tumors. Some of them appear to embody, at least, portions of the truth: they point to subordinate causes which are at work in individual instances, and which need a central principle to unite them into a coherent whole. The more important of these hypotheses must be briefly considered.

1. Theory of Embryonic Remains.—Virchow discovered in the cancellous portions of some of the long bones small "islands" of unaltered cartilage-cells, which he suggested might form the starting-point of tumors. Cohnheim extended this suggestion and applied the principle to explain the origin of all kinds of new-growth. On his hypothesis, instances occur in which either more cells are formed than are necessary for the development of a part, or in the process of growth certain groups of cells are isolated and cut off from their fellows. These groups of superfluous cells may subsequently develop into tumors. The cells may either continue to develop in the ordinary way, so as to form mature tissue-cells of various kinds, or they may remain embryonic in character. In the former case, tumors of the benign variety will arise—resembling adult tissue and growing relatively slowly; in the latter case, malignant growths will occur. In favor of this theory the following facts may be adduced. (1) Dermoid cysts, which are practically innocent tumors, are almost certainly due to errors of development, and congenital moles frequently serve as the starting-points of melanotic sarcomata in later life. (2) Tumors are very frequently found in the neighborhood of points where the developmental process is complicated, and where, therefore, errors might naturally be expected to occur most frequently. Instances are seen in the common appearance of carcinoma in the rectum, where the junction takes place between the original hind-gut and the invaginated epiblast, forming the proctodæum; at the external os uteri, where Müller's ducts open into the urogenital sinus; and at points where different varieties of epithelium meet, as at the cardiac and pyloric orifices of the stomach. (3) In many cases there are formed in various organs tumors consisting of cells of an entirely different character to those normally found in such positions, the presence of which can, however, be accounted for by supposing the inclusion of a portion of some neighboring structure. Thus, for example, parotid tumors frequently contain cartilage, which may be derived from that forming the inferior maxilla (Meckel's cartilage); and renal growths may contain cells resembling those of the

adjacent suprarenal body, or voluntary muscle-cells derived from the embryonic muscle-plates, which lie near the Wolffian body in the process of development.

On the other hand, several objections may be raised to Cohnheim's theory. (1) The "rests" or isolated cell-groups, upon which it is based, are not actually found with any frequency within the body. (2) Those which do occur, such as the cartilage-islands discovered by Virchow, and certain epithelial groups in the tonsils, do not show any actual tendency to develop into tumors—in other words, no transition stages are found between these masses of cells and actual tumors. (3) Tumors do not occur *at* points of fusion between different embryonic structures, but rather *in the neighborhood* of these points, which are in many cases specially liable, owing to their anatomical characters, to traumatism and mechanical irritation. (4) New growths may arise in scar-tissue, in which it is practically impossible to imagine the existence of primordial "rests." (5) Cohnheim himself admitted that certain instances of tumor-formation, in which chemical irritants were obviously the exciting causes, could not be explained on this theory.

The necessary conclusion appears to be that the theory of "embryonic remains," while indicating a method of causation which is probably effective in the case of certain classes of tumor, is not adequate to embrace the whole of the group, and affords only an incomplete and partial explanation.

2. Theory of Chronic Irritation.—Many examples are seen of tumors arising at points which are the seats of chronic inflammation. Thus, the edges of long-standing ulcers are favorite positions for the development of epitheliomata, and the points at which this disease most frequently affects the alimentary canal are those at which the lumen is narrowed, and which are, therefore, specially liable to traumatism from the contents of the tube. Such localities are (1) the two orifices of the stomach, (2) the point where the œsophagus is crossed by the left bronchus, and (3) that where it joins the pharynx, opposite the cricoid cartilage. The large intestine is much more frequently the seat of tumors than the small, possibly owing to the solid nature of the contained fæces, their longer contact with the intestinal wall, and their consequent liability to irritate the mucous membrane: the rectum and anus, where this cause would be most at work, are specially frequent seats of tumor-formation. Various chemical irritants, such as tar and paraffin, may give rise to epithelioma in the skin of the arms of workers engaged in handling them; and soot is apparently the exciting cause of cancer of the scrotum in chimney-sweeps.

When inflammation is produced and maintained experimentally for long periods, it is found that the peculiar form of cell-division (irregular mitosis) characteristic of tumors tend to appear. If the inflammation is allowed to subside, these are again replaced by normal mitotic figures.

On the other hand, the frequency with which instances of chronic irritation occur, and the relative rarity of the appearance of tumors in

connection with them, render it certain that irritation alone cannot be a sufficient cause of tumor-formation. The number of ulcers of the leg, which may be seen every day at a surgical out-patient department, with a history of several years' duration, is alone sufficient proof of the inadequacy of this theory by itself to account for the phenomena.

3. The Parasitic Theory.—The endeavor to find a parasitic organism as the cause of malignant growths has been the guiding principle in the greater part of recent research. When first bacteria were recognized as the cause of a number of diseases, several organisms were isolated, each of which was claimed by its discoverer as the cause of cancer. None of them, however, stood the test of further experience. Parasitic protozoa were next brought forward as the agents concerned. There is a disease of the rabbit due to an animal parasite (*coccidium oviforme*) in which a proliferation of the lining epithelium of the bile-ducts occurs, resembling an adenoma in appearance. This was set up as the type of tumor-formation, and the so-called cancer-bodies (p. 139) were assigned to this class of animalcules. It is probable, however, that the growth in the bile-ducts of the rabbit is inflammatory in origin, and is analogous to certain papillomata of the bladder and larynx in man, which are produced by chronic irritation. The identification of cancer-bodies with protozoa is not now supported by many authorities, and champions of the parasitic theory are in favor of regarding these peculiar bodies as parasitic yeasts (*blastomycetes*). Plimmer has cultivated from carcinomata a fungus which is capable, when injected into the peritoneal cavity of animals, of causing nodular proliferations of the endothelial cells of the serous membrane. Schueller and Schmidt also claim to have isolated and cultivated specific organisms from cancers; but their researches need confirmation. Doyen has isolated a micrococcus which he calls *M. neoformans*, and believes to be the causal agent.

It may be pointed out in favor of the probability of a parasitic origin of malignant growths (1) that they tend to occur in old persons rather than in the young or adult, just as parasites attack weakly rather than strong individuals; and (2) that the dissemination of malignant secondary growths, by blood- and lymph-channels, bears a considerable resemblance to the spread of a process such as tuberculosis. If it were satisfactorily proved that the peculiar cancer-bodies were in reality parasites, which occurred only in this disease, a fairly strong *prima facie* case would exist for believing in this theory. This proof does not yet exist, many observers holding that these appearances are only masses of hyaline material, fragmented nuclei, leucocytes, vacuoles, or invaginated cells.

Against the theory, on general grounds, cogent arguments may be urged. (1) There is practically no evidence—either clinical or experimental—of infection taking place between different individuals; nor does the disease appear in epidemic or endemic form. Instances of the occurrence of cancer in several successive inmates of certain houses (cancer-houses) are not proved to be more than coincidences. (2) The method of spread by secondary growths when closely examined is unlike

that in any known infective disease. Thus, a parasite might set up irritation in the tissues with which it came into contact, and thereby cause proliferation of the cells affected. It might thus stimulate either connective-tissue cells alone, as is the case with the bacteria causing inflammation, or it might cause multiplication of the essential cells of organs attacked. As the parasite became distributed throughout the body, it would cause, in the former case, connective-tissue growths in various parts, or, in the latter, growths differing according to the organs invaded. In tumors, on the contrary, the secondary deposits exactly resemble the primary growth, whatever the parts may be in which they are situated. From this it almost certainly follows that they are due to embolism by fragments of the original growth. Such an occurrence is not known to take place in any recognized parasitic disease. (3) Further, no observer has applied the parasitic theory to all tumors alike, nor has any one succeeded in finding cancer-bodies in all specimens of cancer examined. The parasitic theory is not at the present upheld by many pathologists.

4. Theory of Altered Tissue-Resistance.—It has been suggested that tumors are due to an alteration in the mutual relations of tissues, from which it results that one kind of cell overcomes the resistance of neighboring parts and grows more luxuriantly. Thus it is said that in old age the connective tissues suffer from depressed vitality, while epithelium is still vigorous: hence the appearance of carcinomata in advanced life. It is an obvious objection that sarcomata—connective-tissue tumors—may also occur in old age; and that senile atrophy of the more highly differentiated cells is generally accompanied by an increased growth of connective tissue. Ribbert has, on the other hand, suggested that carcinoma is due, not to overgrowth of epithelial cells, but to upward spread of connective-tissue masses, whereby clusters of epithelial cells are enclosed—the latter merely pursuing their natural process of development. The appearance of secondary deposits seems scarcely explicable on this hypothesis.

5. Theory of Nervous Influence.—It has been suggested that the nervous system has some connection with the origin of new-growths. In favor of such connection may be adduced: (1) the supposed greater frequency of tumor-formation in man and the higher animals than in those lower in the scale—the development of tumors being thus *pari passu* with that of the nervous system; (2) the absence of nerves from tumors; (3) the facts that tumors have no function and that they grow independently of the other parts of the body, often flourishing luxuriantly while the rest of the organism is much emaciated—the latter peculiarity appearing to depend on some freedom from nervous control. (4) It may also be noted that the growth known as *molluscum fibrosum* appears definitely connected with nerve distribution, and that alterations in neighboring nerve trunks have been found in certain cases of sarcoma (Campana). Cheatle has shown that in many instances rodent ulcer and cutaneous carcinoma tend to appear at Head's "maximum points" of nerve distribution, and to limit their extension to areas supplied by particular nerves. So little is known, however, of the action

of the nervous system on the tissues that this hypothesis is at present somewhat visionary.

Conclusions.—From the preceding considerations it seems legitimate to draw the following conclusions: (1) Some tumors arise from developmental errors or cell-rests. (2) Other tumors owe their origin to chronic tissue-irritation. (3) It is possible, but not proved, that the source of irritation may in some cases be a parasitic organism. It remains to consider whether any general principle can be found to connect together these apparently diverse causes.

It is well known that chronic irritation of tissues is accompanied by continual attempts at repair on the part of the tissues, which attempts are constantly interrupted by the irritant. In other words, there is irregular cell-multiplication. An example of this may be seen at the margin of a chronic ulcer. Here microscopical examination shows that there occur masses of epithelial cells embedded among the granulation-tissue, and cut off from the surface-epithelium in which they originated. It requires no great stretch of imagination to see in such isolated cells rudiments of potential tumors, analogous to the developmental "rests" which are recognized as the other great source of new-growths. If this be so, *tumors may be said to originate in groups of cells which have become severed from their natural connections in the body*, whether this be the result of developmental errors or of other causes. What exactly is implied by "natural connections" requires further elucidation: it is possible that it is in this direction that we may look for the action, or failure of action, of the nervous system, as was suggested above.

Certain experiments supply facts to some extent favoring this suggested explanation of the origin of tumors. Thus Birsch-Hirschfeld and Garten injected emulsions of living embryonic cells into the livers of adult animals, and found that in some cases definite tumor-like growths resulted. These, however, did not persist, but were ultimately absorbed. Further, Lack has described an experiment by which cells from the ovary of a rabbit were set free in its peritoneal cavity, and as the result of this a definite carcinomatous mass with secondary growths developed. Taken together, these experiments appear (if confirmed) to prove that free embryonic or epithelial cells set free in the tissues may form tumors. Further, they throw some light on the possible nature of the difference between benign and malignant growths. In the first-mentioned series of experiments it was found that only cells from young embryos were capable of the development described: those from more advanced fœtuses were merely absorbed by the tissues. This appears to indicate that, in order that tumors may develop, a certain relation must exist between the vigor of the aberrant cells and that of the surrounding parts. If the free cells are vigorous and the tissues comparatively non-resistant, a rapidly growing tumor will result: this will infiltrate surrounding tissues, and portions will be easily carried away to form secondary deposits. If, on the other hand, the tissues are more resistant, the invading cells will grow slowly and with difficulty, and there will be time for a capsule of connective tissue to be

formed around them: the tumor will then be an innocent one, as in the case of an implantation cyst. Should the resistance of the tissues be subsequently weakened, innocent growths may become malignant, as is not infrequently seen to occur. Finally, if the resistance of the tissues is sufficient, any cells which are accidentally set free are absorbed and not permitted to establish a footing. This is presumably the case with the majority of mankind, who are exposed to the cause of tumor-formation equally with the minority who develop the disease: only those whose tissues are of feeble resisting power against invading cells become the subjects of new-growths. Simple traumatism, such as blows, to which many patients attribute the origin of their trouble, may be the agent by which cells are torn from their connections and allowed to take on independent growth.

Beard has suggested that the cells which go astray are the primordial germinal cells, formed by the chorion and homologous with the spores of sporozoa. One of these cells develops into the fœtus: the others are enclosed within its tissues, making their way to the ovary or testis, as the case may be, to become sperm-cells or germ-cells. If one of these cells go astray and fail to reach the proper reproductive organ, it may lodge elsewhere and develop into a tumor. The occurrence of special mitoses in tumors is in harmony with this theory (Grünbaum).

Classification.—In our present state of ignorance no satisfactory classification of tumors is possible. The one here adopted is based upon their histological characters. Tumors arising from *mesoblastic* tissues are arranged in three groups: the *first*, resembling the most highly differentiated tissues; the *second*, the ordinary connective tissues; and the *third*, the embryonic tissues. In dealing with tumors from *epiblastic* and *hypoblastic* tissues the same order is followed.

For the sake of convenience, all cysts are grouped together at the end of the section dealing with tumors—though the great majority of cysts are not new growths.

Classification of Tumors.

Mesoblast.

I.—*Type of Higher Tissues.*

Type of muscle	Myoma.
Type of nerve	Neuroma.
Type of bloodvessels	Angioma.
Type of lymphatic vessels	Lymphangioma.

II.—*Type of Fully Developed Connective Tissues.*

Type of fibrous tissue	Fibroma.
Type of mucous tissue	Myxoma.
Type of adipose tissue	Lipoma.
Type of cartilage	Chondroma.
Type of bone	Osteoma.

III.—*Type of Embryonic Connective Tissues.*

The varieties of Sarcoma.

IV.—*Type of Epithelial Tissues.*

Epiblast and Hypoblast.	Papillæ of skin or mucous membrane	Papilloma.
	Glands	Adenoma. Carcinoma.
	Fœtal membranes	Chorio-epithelioma.

V.—*Teratomata, or Congenital Mixed Tumors.*

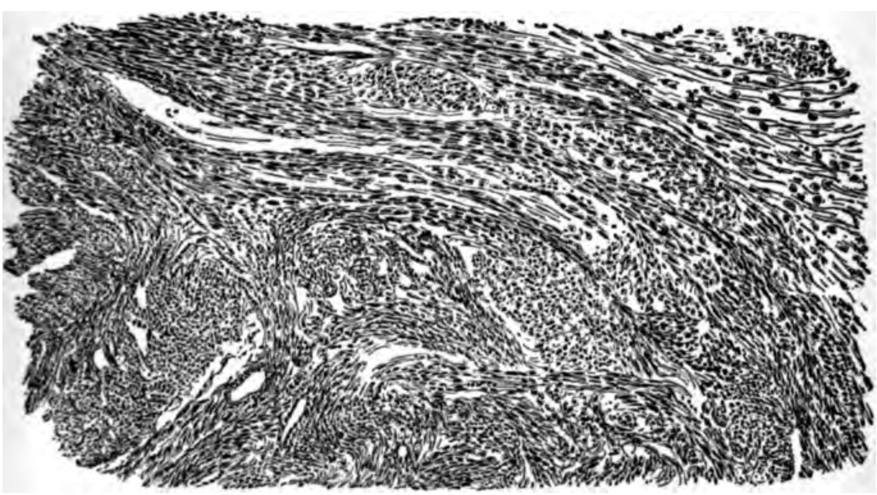
MYOMA.[1]

Myomata are tumors consisting of muscular tissue. There are two varieties—*rhabdomyoma* and *leiomyoma.* (Fig. 42.)

1. **Rhabdomyomata** consist of striated muscle combined with varied but generally considerable amounts of connective tissue. They are congenital and very rare. The kidney and testis are the commonest sites. The striated muscle-cells in congenital growths of these organs are probably due to the original inclusion, in the Wolffian body, of cells from the adjacent muscle-plates.

2. **Leiomyomata** consist of non-striated muscle-cells, more or less isolated or grouped into fasciculi of various sizes, with a varying

FIG. 42.



Myoma of uterus, showing the interlacing bundles of muscle-cells running in all directions. × 90.

quantity of connective tissue and bloodvessels (Fig. 42). The muscular elements either present an approximately regular arrangement, or pass in all directions through the tumor. The bloodvessels, which usually are not numerous, are distributed in the connective tissue.

Leiomyomata are most frequent in the uterus; they also occur in the prostate, the œsophagus, the stomach, and the intestines. They frequently become pedunculated and form polypi. They are much

[1] Greek μῦς, a muscle; ῥάβδος, a rod; λεῖος, smooth.

commoner than the striated growths, and are probably strictly homologous. They may form distinctly circumscribed tumors surrounded by a fibrous capsule, or ill-defined irregular masses in the midst of the muscular tissue in which they grow.

The most frequent **secondary change** which myomata undergo is *calcification*. *Hemorrhage, mucoid softening*, and the consequent formation of cysts are occasionally met with; also *inflammation, ulceration*, and *necrosis*.

Clinically, myomata are benign growths, but rare instances of malignant leiomyomata have been recorded.

Myoma of Uterus.—The uterus is by far the most frequent seat of myomata, and here they constitute the so-called "*uterine fibroids*." In most of these muscular tumors of the uterus there is a large proportion of connective tissue—hence the terms "fibroid" and "fibromyoma." This is the case especially in older growths. Those newly developed, on the other hand, consist almost entirely of true muscular tissue. These tumors are often multiple. They either form firm, hard masses embedded in the uterine walls, or project into the uterine or abdominal cavities, thus forming the intramural, subperitoneal, and submucous varieties. When projecting into the uterus they constitute a common form of *uterine polypus*. They do not form till after puberty, and are commonest in elderly sterile females. Their growth is usually slow. Pregnancy causes them to enlarge rapidly, and they undergo some involution after delivery. They generally atrophy at the menopause. The older ones are liable to become calcified. They also sometimes undergo mucoid softening, which gives rise to the formation of cysts in their interior; or they may be the seats of necrosis and suppuration.

NEUROMA.

Neuromata are tumors consisting of nerve-tissue, and are among the rarest of new-growths.

They are usually made up of a mass of ordinary medullated nerve-fibres; they, therefore, resemble the cerebrospinal nerves in structure. Virchow has also described, as exceedingly rare formations, tumors composed of non-medullated fibres and of ganglionic nerve-tissue. Neuromata are generally small, hard, and single tumors. They always originate from pre-existing nerve-tissue, which fact determines their site. Clinically, they are described as innocent, painful, and of slow growth.

Recent investigations have shown that most tumors, formerly described as neuromata, are really fibrous, fatty, or myxomatous growths occurring in connection with nerves, and so distributed among the nerve-fibres that it is difficult to ascertain whether any new growth of nerve-tissue has occurred other than elongation of the pre-existing nerve-elements. Most of the small, hard, painful tumors occurring in connection with nerves are probably fibromata. Of similar nature are the plexiform masses found in the skin and subcutaneous tissue, and known to be hereditary (see p. 107).

The term *amputation-neuroma* is applied to the bulbous ends of nerves sometimes found in stumps. They consist of fibrous tissue containing masses of rolled-up nerve-fibres—attempts at repair rather than tumors. They are usually connected with the cicatricial tissue of the stumps.

GLIOMA.[1]

Gliomata are tumors composed of neuroglia-tissue. The cells are similar to the stellate or spider-shaped cells with large nuclei, which normally form this tissue, but they may be so packed that their processes are hidden: the microscopic appearances of the tumor are, therefore, not unlike those of a round-celled sarcoma. In other cases the cells are comparatively few and their processes distinct, so that their structure resembles that of a myxoma. The vessels vary in number and size, and are frequently supported in fibrous septa derived from the pia mater. The adventitia of the vessels is generally thickened and may often undergo hyaline changes.

To the **naked eye**, these tumors are of almost the same consistency as the brain-substance, but generally of a grayer color. As in other tumors, the larger the proportion of cells the softer is the tumor. Although gliomata grow slowly, they are not encapsuled; and although they progressively infiltrate the tissues, they do not give rise to secondary growths unless they take on distinctly sarcomatous structure.

Among the **secondary changes** that may be found in these growths are small *hemorrhages* into their substance; they may also undergo *fatty degeneration* or *cystic* changes.

Gliomata **originate** in those parts which are outgrowths of embryonic cerebral vesicles—*i. e.*, brain, spinal cord, optic nerves, retina, and olfactory lobes. In the spinal cord the tumor grows along the periependymal tissue around the central canal, giving rise, as its cells soften and break down, to the condition known as "*syringomyelia*."

Clinically, these growths are innocent, though they may occasionally become sarcomatous.

ANGIOMA.[2]

Angiomata—called also "hæmangiomata," to distinguish them from lymphangiomata—consist of bloodvessels held together by a small amount of connective tissue.

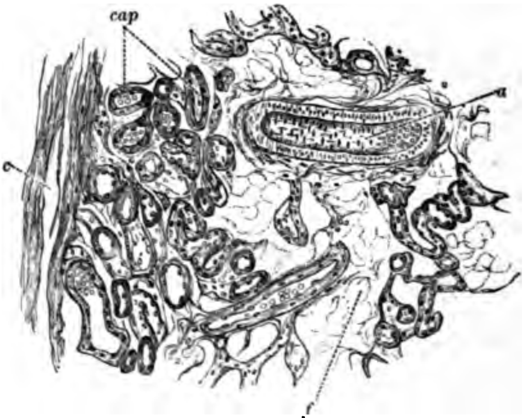
They may be divided into two **varieties**, (1) *simple* or *capillary* angiomata, made up of new vessels roughly resembling ordinary bloodvessels; and (2) *cavernous* angiomata, consisting of a cavernous structure similar to that of the corpus cavernosum of the penis.

1. **Capillary Angiomata.**—These tumors consist of a mass of bloodvessels, including arteries, veins, and capillaries in various proportions, bound together by a small quantity of connective tissue and fat. The lumen of the vessels may be cylindrical, sacculated, or fusiform. The thickness of the walls varies, those of the capillaries being often much thicker than is usual in normal vessels (Fig. 43).

[1] Greek γλία, glue. [2] Greek ἀγγεῖον, a vessel.

These growths occur principally in the skin and subcutaneous tissue: in the former, they give rise to the common *cutaneous nævi*, and the so-called *port-wine stains* or *mother's marks;* in the latter, they form soft, spongy tumors imparting a bluish color to the overlying skin. They

FIG. 43.



Capillary nævus from subcutaneous tissue of a child. Vessels of new growth: *a*, normal artery; *f*, fat-cells; *c*, capsule; *cap*, capillaries with thickened walls × 100. (Boyd.)

are probably always congenital, though they may not be noticed for a few weeks after birth.

Capillary angiomata are often combined with other growths, such as lipoma, glioma, or sarcoma. Sometimes cysts containing altered blood form in them: these are probably due to hemorrhage.

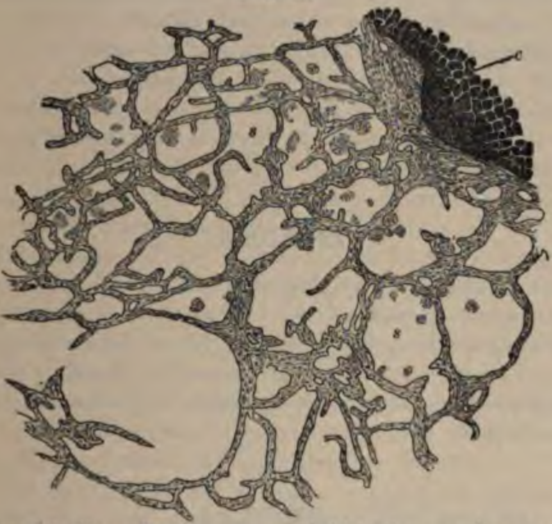
2. Cavernous angiomata are made up of irregular fibrous alveoli, which communicate freely with one another, and are lined with an endothelium similar to that of the veins (Fig. 44). These spaces are distended with blood, which is supplied to them by numerous tortuous vessels and circulates with varying degrees of rapidity. The arteries open directly into the spaces. These growths are commonly of a bluish color, and may be diffuse or form distinctly circumscribed tumors, sometimes exhibiting distinct pulsation. Their favorite seat is the skin and subcutaneous tissue; but they may also occur in the orbit, muscles, liver, spleen, and kidneys. They may develop by dilatation of the vessels of a simple angioma. They may be congenital; but in the liver Ziegler thinks they develop after middle age, when the cells begin to atrophy.

Cirsoid Aneurism.—This term is applied to a change in the arteries of an area, especially on the head, by which they become dilated, greatly elongated, and tortuous; it is doubtful if new vessels are formed. Some cirsoid aneurisms are congenital; others follow injuries.

Angiomata—both capillary and cavernous—are frequently found in the neighborhood of embryonic clefts—either facial or branchial—as well as at the orifice of the urethra (*urethral caruncle*). In other cases their position seems to correspond with nerve distribution: thus, cutaneous

angiomata (*nævi*) may be found limited to the area of distribution of one branch of the fifth nerve. In a large number of cases, however, the position of angiomata does not conform to either of these rules.

FIG. 44.



Cavernous nævus of the liver. From a woman aged thirty-nine. *s*, *s*, large spaces bounded by fibrous walls, some containing blood-débris; *c*, liver-tissue toward which the growth is bounded by thick fibrous walls. × 30. (Boyd.)

According to Thoma, the formation of the new vessels is dependent upon variations in the relationship which the intravascular pressure bears to the normal pressure exerted on the vessels by the tissue concerned. He further points out that when the different orifices of the body are being formed various internal parts become external, and *vice versa*. In this way the relative pressure in different parts is liable to considerable alteration, and local growths of new vessels may, according to Thoma's hypothesis, easily occur. The same observer has shown that in fœtal life the growth of the section of a vessel is proportionate to the rate of flow through it, and that the lumen of the new vessels will be large or small accordingly.

Pearce Gould considers that in many cases *varicose veins* are of the nature of angiomata.

LYMPHANGIOMA.

Lymphangiomata are tumors consisting of abnormally large lymphatic vessels. It is doubtful how much of the growth is due to simple dilatation and how much to new formation of lymphatic vessels. Strictly speaking, very few lymphangiomata are "tumors." The divisions are the same as those of angioma—**capillary** and **cavernous**. A section of the latter would scarcely be distinguishable from one of cavernous nævus (Fig. 44), except by the contents of the spaces. There is generally fat in the stroma.

Each kind may be congenital or acquired. *Congenital* dilatations are found in the tongue (macroglossia), lip (macrocheilia), and labium, causing hypertrophy of the parts. They are also found in other parts of the skin.

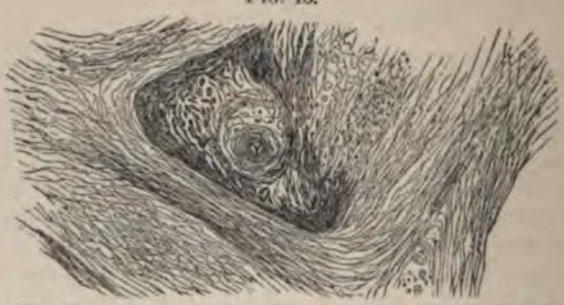
Acquired dilatation of lymphatics is found in the skin and subcutaneous tissue, especially of the thigh and thorax. In this way tumors as large as an orange may be formed in the subcutaneous tissue. Dangerous loss of lymph may occur from rupture of one of the vessels. Fibroid thickening may take place in the parts from which the lymphatics pass to the tumor, which in the skin may assume the appearance of a wart.

FIBROMA.

Fibromata or tumors consisting of fibrous tissue.

The **fibres,** which constitute the chief part of the growth, are either loosely or densely packed, and are arranged in intersecting bundles of various sizes or in whorls around the bloodvessels (Fig. 45): in many cases no definite arrangement is recognizable. Yellow elastic fibres are very rarely met with.

FIG. 45.



Fibrous tumor from the skin. Near the cut bloodvessel, V, are seen some cells; also fibres cut transversely. × 100.

The **cells,** like those of normal fibrous tissues, are generally few in number, and are usually most abundant around the vessels. They are minute, spindle-shaped, fusiform, or stellate bodies, with processes of varying length, which communicate with similar processes from neighboring cells. The cells vary in size and number with the rapidity and age of growth—the slower and older the growth, the denser the tissue, and the flatter and less numerous the cells.

Fibromata usually contain but few bloodvessels. In the softer growths, however, these are often more numerous, and may form an important constituent of the tumor (*fibroma teleangiectaticum*, *angio-fibroma*). Dilated veins sometimes form a cavernous network, the walls of which are firmly united to the tissue of the tumor, so that if divided or ruptured they are unable to retract or collapse, and profuse hemorrhage may ensue (*fibroma cavernosum*).

Partial *mucoid softening* and *calcification* are the most common **secondary changes**; *ossification* takes place in fibromata springing from bone. *Ulceration* also sometimes occurs in those growths which are situated in the skin and submucous tissues.

Fibromata **originate** from *connective tissue*, from the cutis or subcutaneous tissue, from submucous or subserous tissue, from fascia, from periosteum, from neurilemma, or from the connective tissue of organs.

Clinically, fibromata are perfectly innocent: they grow slowly, and do not recur after removal.

Fibromata are generally divided into **two varieties**, *soft* and *hard*, corresponding to, and usually originating from, the loose and dense varieties of ordinary connective tissue respectively.

1. **Soft Fibromata.**—These consist of the looser and less dense form of fibrous tissue. They are met with as diffuse growths in the subcutaneous and submucous tissues. In the former situation they often form large pedunculated and non-encapsuled tumors, which are commonly known as *wens*. These are sometimes multiple. An extensive thickening of the skin and subcutaneous tissue over one or more limbs sometimes occurs, producing large masses which hang down from the thighs, buttocks, and other parts (*elephantoid fibroma*).

In addition to these diffuse growths, more circumscribed and encapsuled fibrous tumors of the soft variety are occasionally met with, growing from the scalp, scrotum, labium, intermuscular septa, or other situations.

2. **Hard Fibromata.**—These are composed of dense fibrous tissue like that in tendons. They are firm, hard, encapsuled tumors, presenting on section a grayish-white, glistening, fibrous appearance. These tumors often occur in connection with bone—especially the upper and lower jaws—originating either in the centre of the bone or in the periosteum. Growing from the periosteum of the alveolus they constitute simple *fibrous epulis*. They are also met with in the nasopharynx, springing from the front of the spine, or from the base of the skull. In these firm fibrous growths the veins may form cavernous spaces.

Some old tumors of the uterus are almost pure fibromata; but the so-called uterine "fibroids" are in most cases local overgrowths of the involuntary muscular tissue of the organ (p. 102).

Tumors consisting mainly of hard or soft fibrous tissue are frequently met with in the breast; but in this situation they always contain at least a few foci of proliferated gland-tissue, and are generally described as *adenofibromata* (p. 132).

Warts (p. 129) and *nævi* (p. 104) are sometimes classed as fibromata.

Neurofibromata (*False Neuromata*).—These hard fibrous tumors most frequently occur in connection with the superficial nerves. They grow from the perineurium and endoneurium, and as they increase in size the nerve-fibres become expanded over or buried in them. They are very firm, rounded tumors, and are frequently multiple and hereditary. The function of the nerves is not necessarily affected.

Small wart-like projections from the skin, consisting of soft fibrous tissue, grow in connection with the sheaths of cutaneous nerves (von Recklinghausen), and are known as *molluscum fibrosum*. They are probably, therefore, neurofibromata.

Fibropsammomata.[1] — These are soft fibrous growths containing large numbers of concentrically laminated calcareous masses, already described as *corpora amylacea* (p. 74). They give rise to the so-called "brain sand"—hence the name of the growth.

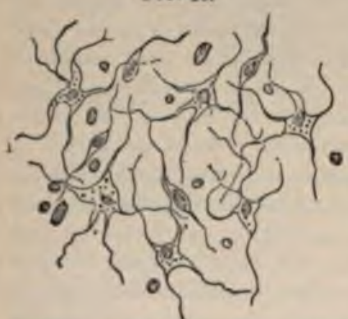
Psammomata grow from the pineal gland, the membranes of the brain, or the choroid plexus. In the last-named structure a psammoma often contains numerous cysts. Such growths are of no pathological importance except when of sufficiently large size to produce symptoms by pressure.

Cheloid.[2]—The peculiar formation known as Cheloid bears some resemblance to a tumor. It is, however, more probably the result of a chronic inflammatory process. The growths occur as hypertrophic masses of scar-tissue, starting from natural scars left after wounds, especially when the incision does not correspond with the natural "lines of cleavage" of the skin. They may attain considerable size and give rise to much disfigurement. So-called "spontaneous cheloids" probably originate in slight injuries which are overlooked.

MYXOMA.[3]

Myxomata consist of mucous tissue—*i. e.*, a fragile connective tissue of which the intercellular substance is translucent, homogeneous, and jelly-like, containing much fluid, and yielding mucin. Physiologically, this tissue is met with in the *vitreous body* of the eye, in which the cells are roundish and isolated; and in the *umbilical cord*, in which the cells are fusiform or stellate, and give off fine anastomosing prolongations. All embryonic connective tissue, especially that which subsequently becomes adipose, possesses an intercellular substance containing much mucin. New formations may undergo mucoid degeneration, and thus closely resemble myxomata in their physical and chemical characters; but a myxoma consists of mucous tissue from the first. Myxomata are thus very closely allied to sarcomata, and by many are included in the same class of new formations. An œdematous fibroma or lipoma closely resembles a myxoma or myxolipoma.

Fig. 46.



Myxoma. From the arm; showing the characteristic branched anastomosing cells, a few leucocytes, and one or two spindle-cells. × 200.

[1] Greek θάμμος, sand. [2] Greek χήλη, a claw. [3] Greek μύξα, slime.

Structure.—The majority of the cells are angular and stellate, with long anastomosing prolongations; others are isolated, and fusiform, oval, or spherical in shape (Fig. 46). Their contour is very indistinct, owing to the refractive nature of the intercellular substance. The latter is very abundant, perfectly homogeneous, soft, gelatinous, viscid, and yields large quantities of mucin: in it are a varying number of amœboid cells. Bloodvessels are not numerous, and are readily visible and easily isolated. A few elastic fibres are sometimes seen between the cells.

To the **naked eye**, myxomata are of a peculiar soft gelatinous consistence, and of a pale grayish or reddish-white color. Their cut surface yields a tenacious mucilaginous liquid, in which may be seen the cellular elements of the growth. They are usually separated from the surrounding structures by a very thin fibrous capsule. Fine prolongations extend from this into the growth, dividing it into lobules of various sizes. In exceptional cases a myxoma may increase by the continuous invasion of the surrounding tissues.

Among the **secondary changes** the most common are rupture of the capillaries, *hemorrhage*, and the formation of *blood-cysts;* these, however, are less frequent than in sarcomata. The cells themselves may undergo *mucoid* or *fatty degeneration*, and thus be destroyed: this is usually accompanied by liquefaction of the intercellular substance. The growth is liable to *inflammation*, *ulceration*, and *necrosis*.

The **varieties** of myxoma depend principally upon its combination with other growths; a pure myxoma is very unusual. The most common combination is a myxolipoma. Combinations with sarcoma, fibroma, chondroma, and adenoma are also met with.

Myxomata **originate** from *connective tissue*, and are most common in subcutaneous and subserous fat, and in submucous and intermuscular tissue. They also grow from the periosteum and medulla of bone, from the connective tissue of organs (especially the breast), and from the perineurium of nerves, forming one variety of *false neuromata*. They may grow from the placenta, constituting the so-called "uterine hydatids."

When situated in superficial parts they may become pedunculated. They are usually said to constitute one form of *nasal polypus;* these growths, however, most frequently result from chronic catarrh, and are inflammatory overgrowths rather than true tumors. In the skin myxomata are often papillary.

Clinically, myxomata occur chiefly after midlife, and are, for the most part, benign. Their growth is usually slow, but they may attain an enormous size. If completely removed they rarely recur. Sometimes, however, they recur locally after removal, but they probably never reproduce themselves in internal organs. In speaking of their malignancy, their occasional association with sarcomata must be borne in mind.

LIPOMA.[1]

A lipoma, or fatty tumor, is a localized and circumscribed formation of fat.

Lipomata resemble in their **structure** adipose tissue (Fig. 47). They consist of cells containing fat, and a variable quantity of common connective tissue. The cells are like those of adipose tissue, though usually somewhat larger. The nucleus and protoplasm are so compressed against the cell-wall by the fluid contents that they are readily visible only when the cell is atrophied and contains less fat (Fig. 9, p. 41). More or less connective tissue unites the cells into masses or lobules which are larger than in normal adipose tissue, and forms in most cases around the tumor a thin capsule more firmly adherent to surrounding parts than to the tumor, so that the latter shells out easily. Bloodvessels are distributed in the fibrous septa. Mucous tissue is often associated with the fatty (*myxolipoma*).

FIG. 47.

Lipoma. Some of the cells contain crystallized fatty acids. × 200.

To the **naked eye**, lipomata are more or less lobulated, and usually surrounded by a fibrous capsule. When subcutaneous they move freely over the deep fascia; but often the attempt to raise the skin from them causes it to dimple, showing that they are adherent to it. On section, they present the ordinary appearance of adipose tissue, with more or less dense fibrous septa between the lobules. Their consistence and their adhesion to the capsule vary with the amount of fibrous tissue which they contain. In their growth they occasionally become pedunculated.

Secondary changes in lipomata are not common; their fibrous septa may, however, become *calcified*, or even *ossified*. Softening may occur occasionally from *mucoid* change. *Inflammation* is rare; but when they are large and situated in the subcutaneous tissue the skin over them may become adherent, and *ulceration* and *necrosis* of the tumor occur.

The chief **varieties** are *fibrolipomata*, in which the fibrous tissue is excessive, and *myxolipomata*, or combination of mucous with fatty tissue, and *nævo-lipomata*, in which an angiomatus development of vessels is seen. For *liposarcoma*, see p. 118.

Lipomata **originate** from *connective tissue*, and their possible distribution is almost coextensive with that of adipose and connective tissue. They occur most frequently in the subcutaneous tissue of the trunk, especially of the back and abdominal wall; sometimes in intermuscular septa, subsynovial and subserous tissues; and occasionally also in the submucous tissue of the stomach and intestines, and even in internal organs where there is normally no fat.

[1] Greek λίπος, fat.

Clinically, lipomata are quite innocent; they grow slowly, but may attain a huge size; they are usually single, but are not infrequently multiple and hereditary. Sometimes they change their position considerably, presumably from the influence of gravity. However emaciated the individual may become, the fat of a lipoma is but slightly diminished, and never under any circumstances disappears.

CHONDROMA.[1]

A chondroma is a tumor composed of cartilage.

In **minute structure** these tumors consist of cells and of intercellular substance, both of which present all the variations observed in normal cartilage. The *intercellular substance* may be hyaline, fibrous, or mucoid. When fibrous, the fibres may be arranged like those of fibro-cartilage, or more or less concentrically around the cells, as in the reticular cartilages of the ear and larynx. The fibres may be distinct or hardly perceptible. When hyaline or mucoid, the intercellular substance is sometimes quite soft in consistence. The cells may be round, fusiform, or stellate, and numerous or few, in proportion to the matrix. In the fibrous form they are often small, and somewhat like those of connective tissue; in the hyaline forms they are usually large, and round or oval (Fig. 49); and in the rarer mucoid forms they are more commonly stellate and branched, like the transitional cells at the edge of articular cartilages where the synovial membrane ends. The cells

FIG. 48.

Ossifying chondroma of femur. *a*, cartilage-cells; *b*, cells near surface of tumor, resembling those seen in osteoid tissue (p. 112); *c*, calcifying matrix. × 125.

occur singly or are arranged in groups, and are usually surrounded by a capsule, as in normal cartilage, although this is often very indistinct. A cell possesses one or more nuclei surrounded by granular protoplasm; sometimes a cell-wall cannot be distinguished.

To the **naked eye**, the *more slowly growing* chondromata are hard or slightly elastic tumors, smooth or lobulated, and seldom exceeding the size of an orange. They are encapsuled, and consist either of a

[1] Greek χόνδρος, cartilage.

single tumor or of several smaller masses held together by fibrous tissue in which the few bloodvessels run. On section, they present the appearance and consistency of cartilage, frequently modified by one or other of the secondary changes mentioned above. The appearances may be those of a fibroma, the cartilage-cells being unrecognizable without the aid of the microscope.

The *more rapidly growing* forms, such as often start from the pelvic bones or ribs—myxochondromata, osteochondromata and chondrosarcomata—are much larger, softer, and more vascular, and never present the appearance of pure cartilage; only a few islets at most will be distinct in the soft grayish tissue, which is not separated by any capsule from the adjacent tissues.

Calcification is the most common **secondary change.** It affects with peculiar frequency the largest group of chondromata—those of the phalanges and metacarpal bones of the hands. It spreads from many centres, commencing in the capsules, and then involving the intercellular substance. *Ossification* is especially frequent in chondromata which grow near the junction of the epiphyses and shafts of long bones (Fig. 48). These ossify as they grow and form pedunculated exostoses. The common subungual exostosis of the great toe is generally an ossifying fibroma, chondroma, or fibrochondroma. Fatty degeneration and mucoid softening are common changes, and may lead to the formation of large softened masses which present the appearance of cysts. In rare cases the skin covering the tumor ulcerates, and a fungating mass protrudes.

FIG. 49.

Hyaline chondroma. × 200.

The **varieties** of chondroma depend upon the nature of the intercellular substance, and are, therefore, fibrous, hyaline, and mucoid: these are often combined in the same tumor. As a rule, those originating from the medulla of bone are of the hyaline and mucoid class, whilst those originating from connective tissue in other situations are more frequently fibrous. The rapidly growing fibrous forms approach very closely to, and merge with, the sarcomata (*chondrosarcoma*), while the mucoid forms resemble the myxomata (*myxochondroma*); and these two kinds of growth are often associated in the same tumor. Chondromata are rarely homologous in the strict sense (p. 89), and when associated with sarcomata are malignant.

A variety of chondroma has been described under the name of *osteochondroma*, which in structure more closely resembles bone than cartilage. It consists of a tissue similar to that met with between the periosteum and bone in rickets, which, from its resemblance to osseous, has been called *osteoid* tissue. This only requires calcifying to become true bone. Like bone, it is made up of trabeculæ and medullary spaces; but the trabeculæ, instead of being formed of bone-corpuscles and lamellæ, consist of small angular cells without a capsule, situated in an obscurely

fibrillated matrix, which in part is calcified. The medullary spaces contain a fibrous stroma and many bloodvessels. Osteochondromata, although consisting mainly of this osteoid tissue, contain also a small proportion of cartilage. They originate beneath the periosteum, their common seat being the ends of the long bones. Their growth is very rapid, and they often attain an enormous size. They are much more

FIG. 50.

Multiple chondromata of hand. From a child. The replacement of considerable portions of the phalanges and metacarpal bones by a mass of mingled bony and cartilaginous tissue is well shown. (From a patient of Mr. Clinton Dent's. Skiagram by Mr. Swinton. ⅔ nat. size.)

freely supplied with bloodvessels than the ordinary chondromata, and hence they are much less frequently the seats of retrogressive changes. They are especially prone to become ossified, and to be thus converted into true bone.

Chondromata most frequently originate *from common connective tissue and bone (enchondromata), and only rarely from cartilage (ecchondromata).*

About *three-fourths* of them start in connection with bones, growing either *centrally* or *subperiosteally*. Their favorite seats are the bones of the fingers (Fig. 50) and toes, the lower end of the femur and the upper ends of the humerus and tibia. Much less often, the ribs and the hip-bone are attacked. Virchow has shown that islands of cartilage not uncommonly remain in the shafts of bones; and it is probable that many chondromata spring from such islands (p. 95). The tumors generally begin before the ossification of the epiphyses, whilst the bone is actively growing and vascular. *Most of the remaining fourth* occur, in combination with other tissue-elements, as "mixed tumors" in the *parotid* and *testicle*. Cohnheim suggests, as the source of cartilage in the parotid, an aberrant bit of the rudiment of the jaw; Virchow, a piece of the pinna. In the testis a portion of the rudiment of a vertebra may have been included. The intermuscular septa, the subcutaneous tissue of the breast, and the lungs are occasional seats.

Chondromata are sometimes seen on the surface of the articular cartilages, in the larynx and trachea, and on the costal and intervertebral cartilages. They are simply local overgrowths of hyaline cartilage.

Clinically, chondromata are for the most part innocent growths. They are usually single, except when occurring on the fingers and toes, in which situation they are more frequently multiple. The *central* growths of the phalanges and metacarpal bones occur in children, or before ossification is complete: the graver, *subperiosteal*, forms are commoner later on. Chondromata tend to stop growing about the time of puberty—probably when the epiphyses themselves cease to grow.

OSTEOMA.[1]

Osteomata are tumors consisting of bone, either compact or cancellous.

Osteomata are the result of the ossification of *newly formed connective tissue* other than of inflammatory origin. They must be clearly distinguished (1) from the simple *ossification of normally existing tissues*—*e. g.*, costal, laryngeal, or bronchial cartilages, whole muscles (*myositis ossificans*), insertions of muscles (*rider's bone* in the adductor longus tendon), and membranes of the brain; and (2) from similar *ossification of inflammatory tissue*—such as nodes or general thickenings of bones, the sharp stalactitic processes which may grow round an inflamed joint or on the surface of bone, and the smooth round prominences which almost encircle a joint in rheumatoid arthritis. They must be distinguished, also, from *calcareous deposits* in which there is no bone formed (p. 100).

Osteomata are generally divided into two main **varieties**—1. *Homologous osteomata*, subdivided into *exostoses* and *enostoses*, according as they project (i) from the surface or (ii) into the medullary canal of a bone. 2. *Heterologous osteomata.*

1. **Homologous Osteomata.**—(1) **Exostoses** are again subdivided, according to the density of the bone of which they consist, into two kinds—(α) the *compact, ivory,* or *eburnated;* (β) the *cancellous* or *spongy*.

(α) The **compact,** or **ivory, exostosis** grows from periosteum. It

[1] Greek ὀστέον, a bone.

occurs most frequently on the external and internal surfaces of the skull: the orbit is an especially favorite seat. It is also met with on the scapula, pelvis, and on the upper and lower jaws. In the last-named situation it may grow from the dental periosteum. An osteoma growing from the root of a tooth is known as a *dental osteoma*. An *odontoma* is a tumor composed of dentine, or of some other constituent of a tooth or tooth-sac; or it may grow from the root, neck, or crown of a tooth.

Such growths are smooth, low, rounded, wide-based, covered by the periosteum, and continuous with that of the old bone from which they grow. On section, they are throughout of ivory-like density, and they are usually well defined from the adjacent tissue. Microscopically, the lamellæ are arranged concentrically and are parallel to the surface of the tumor; cancellous tissue is absent, and Haversian canals are few and narrow. Some specimens are less dense, the Haversian canals being as numerous as in ordinary compact bone, but less regularly arranged.

(β) The **spongy, or cauliflower, exostosis** is really an ossifying chondroma. It grows from cartilage, usually near the junction of an epiphysis of a long bone with the shaft. It is especially common at the lower end of the femur and at the upper ends of the tibia and humerus. Its outline is less regular than that of the ivory growths; but it is prominent, more or less pedunculated, and, so long as it is growing, covered by a cap of cartilage. When this cap ossifies growth ceases (*osteophyte*). A section shows that the mass consists of spongy bone, directly continuous with the cancellous tissue of the bone whence it springs, and surrounded by a thin layer of compact bony tissue. The medullary spaces may contain embryonic, fibrous, or fatty tissue.

(2) The **enostosis** is a dense bony growth projecting into the medulla, and is very rare. Osteomata sometimes remain imbedded in the cancellous tissue, and are then termed *central osteomata*.

2. Heterologous osteomata are very rare as primary growths. They have been described as occurring in the subcutaneous tissue; but Malherbe has shown reason for believing that such growths are really sebaceous adenomata with ossified stroma (p. 136). Bony tumors have very rarely been found in the brain and cerebellum. Parts of fibromata, lipomata, and chondromata may ossify. The secondary growths of ossifying sarcomata connected with bone often ossify.

The commonest **secondary change** is *inflammation*. Osteomata may also become *carious* or *necrose*. The last change is most likely to occur in ivory exostoses, effecting their separation and cure.

Osteomata generally **originate** from *bone* (*homologous*), commencing in the periosteum, medulla, or persistent islands of cartilage; but *connective-tissue tumors*, apart from bone (*heterologous*), may ossify.

Clinically, osteomata are perfectly innocent tumors. Their growth is very slow. They rarely attain a large size. They are often hereditary and multiple, in which case they usually occur in early life. Osseous growths which exhibit malignant characters are either sarcomata or chondrosarcomata which have undergone partial ossification. From these, true osteomata must be carefully distinguished (p. 125).

SARCOMA.[1]

Sarcomata are tumors consisting of tissue resembling some stage in the development of any of the connective tissues. In the central parts of some of these tumors the structure resembles the most fully developed of these tissues, such as fibrous tissue, cartilage, or bone. In this way a mixed tumor may result.

Structure.—Sarcomata consist of cells imbedded in intercellular substance.

The **cells**, which usually constitute almost the whole of the growth, consist for the most part of simple masses of nucleated protoplasm, rarely possessing a limiting membrane. There are three principal varieties of cell—*round*, *spindle*, and *myeloid*.[2] The round and spindle cells may be either *small* or *large*. The myeloid cells are much larger than the others. They are irregular and multinucleated, varying both in size and in the number and size of the contained nuclei. One cell may have as many as thirty nuclei. Though in any given tumor one form of cell usually predominates, two or more varieties may frequently be associated.

The **intercellular substance** or **stroma** usually exists in but small quantity. *It intervenes between all cells and is as closely connected with them as in ordinary connective tissue.* These points are often relied upon to distinguish certain sarcomata from carcinomata, but they do not always hold good (p. 127).

The stroma may be fluid and homogeneous, or firm and granular, or more or less fibrous, or even chondrified and ossified. On its amount and nature the consistence of the growth depends.

The **bloodvessels** are usually very numerous. The larger lie in the stroma which supports them; the smaller are usually in direct contact with the cells. Their distribution is very irregular, and their walls are often formed by nothing but the cells of the tumor, though a single layer of endothelial cells may separate the blood from the cells. Hence, on the one hand, the ease with which portions of the tumor are carried away in the blood-stream and the tumor thus generalized; and, on the other, the frequency with which the vessels rupture and permit extravasation of blood into the substance of the growth. Lymphatics are unknown.

An examination of the growing border usually shows a great excess of small round cells over all other forms. These cells extend along the connective tissue in all directions, and force themselves between the essential elements of muscles, glands, and any adjacent organs, while these elements themselves become pale, undergo atrophy, and finally disappear (Fig. 51). In the invaded connective tissue many cell-forms are seen, which may possibly indicate multiplication of the fixed cells: it is not known whether such cells help to form the tumor.

In the ordinary examination of a sarcoma, the appearances in the growing edge should not be relied upon, on account of the predomi-

[1] Greek σάρξ, flesh or muscle. [2] Greek μύελος, marrow.

nance in that part of small round cells over those most characteristic of the tumor.

Physical Characters.—Portions of sarcomata which have undergone no secondary changes are soft, semi-translucent, and gray or pinkish-gray. These appearances are best seen near the circumference of the growth, where the zone of actively growing cells may be narrow. The diagnosis—even with the microscope—between a sarcoma, especially a fibrosarcoma, and the different forms of simple connective-tissue tumors may be exceedingly difficult. This is due to the higher development of the central parts of the sarcoma into one or other variety of fully formed connective tissue. Degenerative processes, such as fatty degeneration, and especially hemorrhage, may greatly interfere with the

FIG. 51.

Small portion of a muscle near shoulder, from a case of sarcoma of the head of the humerus, showing passage of small round cells (probably sarcomatous) along the "lines of least resistance," as in diffuse inflammation. Where the cells are thickest the muscle-fibres are obscured or have disappeared. (Boyd.)

usual appearances: the occurrence of hemorrhage may convert a solid tumor into a blood-cyst with a scarcely recognizable wall.

As a rule, the growing edge is ill-defined, there being no sharp line of demarcation between the tumor and the adjacent parts; but sometimes a slowly growing sarcoma may acquire a capsule by stretching around itself the connective tissue of the organ in which it originates.

Secondary Changes.—The most important of these is *fatty degeneration.* This always occurs to a greater or less extent in the older portions of the growth, causing either softening or the production of cyst-like cavities. It is frequently associated with rupture of the blood-vessels and *hemorrhage;* the latter may give rise to the formation of blood-cysts. *Calcification* (Fig. 60, p. 124), *ossification* (Fig. 61, p. 125), and *mucoid degeneration* are less common. The occurrence of calcification, ossification, and pigmentation is influenced by the predisposition

of the matrix from which the growth is produced—thus, calcification and ossification are more prone to occur in tumors originating in connection with bone, pigmentation in those originating from the cutis or eyeball.

Varieties.—Though all sarcomata possess the same general characters, they present histological and clinical differences which serve as bases for their classification.

The principal features which are thus utilized are (1) the predominant form of cell; (2) the nature of the intercellular substance; and (3) the secondary changes to which the growths are liable.

(1) The predominant form of *cell* enables us to distinguish four groups: the *round-celled*, the *spindle-celled*, the *mixed-celled*, in which no one form predominates, and the *myeloid-celled*. Strictly speaking, this last group is one of mixed-celled sarcomata, but though the myeloid cells can never be said to predominate, they are frequently so numerous as to be the most striking objects in the field, when the growth is examined microscopically (p. 125).

(2) The *stroma* may be mucous, fibrous, cartilaginous or bony; hence we may have a *myxosarcoma*, *fibrosarcoma*, *chondrosarcoma*, and *osteosarcoma*.

(3) The *secondary changes*, which sarcomata undergo, serve to distinguish differing forms, inasmuch as the peculiarities are reproduced in the secondary growths. The chief of these are: *melanosarcoma*, characterized by the development of black pigment, and *chloroma*, a very rare form, with green pigment; *liposarcoma*, in which the cells undergo fatty accumulation; and *calcifying sarcoma*, in which calcareous infiltration is marked.

Mode of Growth and Seats.—Sarcomata always spring from connective tissue, and may occur wherever connective tissue is present. It is doubtful whether they start from adult tissue or from some embryonic remnant. Congenital warts and pigment-spots often serve in later life as their starting-points (p. 96). The skin and subcutaneous tissue, fasciæ, periosteum, medulla of bone, and lymphatic glands are the commonest seats of sarcomata.

Clinical Characters.—Sarcomata occur most frequently in early and middle life, and are among the most malignant of new formations. They are especially characterized by their great tendency to extend locally and to infiltrate the surrounding structures, so that they are exceedingly prone to recur *in loco* after removal. Butlin has shown that sarcomata of certain parts almost always affect lymphatic glands at an early stage—viz., sarcomata of the testis, tonsil, lymphatic glands, and some fasciæ. Those of most other parts show no tendency to affect lymphatic glands at all; so that, on the whole, sarcomata present a contrast to cancers in this respect. Like cancers they are very liable to become generalized. The secondary growths occur most frequently in the lungs. *The dissemination is effected by means of the*

blood-stream, and is a natural result of the thinness of the vessel-walls (p. 116). The dissemination of sarcomata is, on this account, sometimes more rapid than that of carcinomata, in which extension in the early stage takes place by the lymphatics, and dissemination by the blood occurs later in the disease. *Secondary* sarcomata usually resemble the *primary* growth, but in exceptional cases the several varieties may replace one another.

It has already been pointed out that the different varieties of sarcoma possesses very different degrees of malignancy. As a rule, the softer and more vascular the tumor, and the less its tendency to form fully developed connective tissue, the greater is its malignancy. The soft round-celled and large spindle-celled varieties are thus usually much more malignant than the firmer, small spindle-celled growths. Many small spindle-celled tumors, after removal, never recur; whilst others recur locally several times, and only ultimately reproduce themselves in distant parts. As a rule, largeness of the spindle-cells, and the existence in many of them of more than one nucleus, are together evidence of special malignancy. Central sarcomata of bone are much less malignant than the subperiosteal varieties; the latter, with sarcomata of the tonsil and testes, and melanotic sarcoma of the skin, being amongst the most malignant of tumors. The presence of a capsule limiting the growth must also be taken into account in judging of the degree of its malignancy. It must, however, be born in mind that encapsuled sarcomata may invade the surrounding structures, giving rise to adjacent, but discontinuous, nodules. The myeloid growths are the least malignant; they may in exceptional cases give rise to secondary growths in internal organs, but "complete" removal gives a very good chance of non-recurrence. This result sometimes occurs with growths having every appearance of malignity.

Round-celled Sarcomata.

These are of softer consistence than the spindle-celled growths, and from their frequent resemblance in physical characters in encephaloid[1] carcinoma, are sometimes known as "medullary," "encephaloid," or "soft" sarcomata. Histologically, they resemble embryonic tissue, consisting mainly of round cells imbedded in a scanty and usually soft, homogeneous, or finely granular intercellular substance (Fig. 52). The cells usually resemble those met with in the most elementary embryonic tissue; less frequently they are bigger, and contain large round or oval nuclei, with bright nucleoli. There is an almost complete absence of fusiform cells, and of the partial fibrillation which is so frequent in the more highly developed spindle-celled variety.

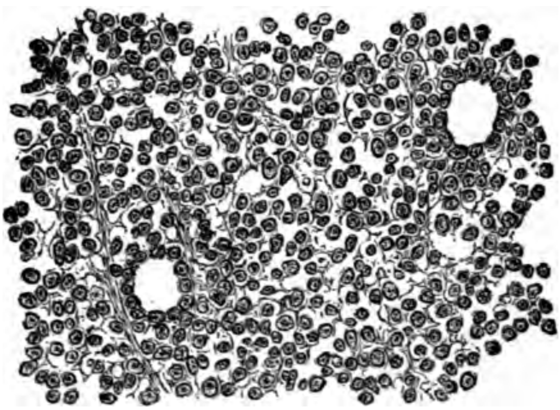
FIG. 52.

Round-celled sarcoma of the liver. × 400.

[1] Greek ἐγκέφαλον, brain.

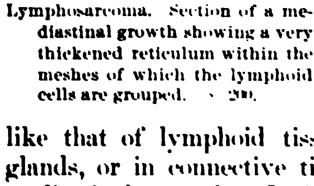
Round-celled sarcomata are of a uniformly soft, brain-like consistence, somewhat translucent or opaque, and of a grayish or reddish-white color. On scraping the cut surface, they yield a juice which is rich in cells. They are exceedingly vascular: the vessels are often dilated and varicose, and, from their liability to rupture, frequently give rise to ecchymoses and to the formation of blood-cysts. The tumors grow from the cutis, the subcutaneous cellular tissue, the periosteum, the fasciæ, and the connective tissue of organs. They extend rapidly by peripheral growth, infiltrate the surrounding structures, reproduce themselves in internal organs, and often involve the lymphatic glands. From their clinical and physical characters these tumors are very liable to be confounded with encephaloid cancer: they are distinguished to some extent by the characters of their cells, but principally by the absence of an alveolor stroma, and by the penetration of the intercellular substance between the individual cells.

FIG. 53.



Lymphosarcoma of the mediastinum, showing cells, reticulum, and bloodvessels. The walls of the latter are formed principally of sarcoma-cells. × 400.

FIG. 54.



Lymphosarcoma. Section of a mediastinal growth showing a very thickened reticulum within the meshes of which the lymphoid cells are grouped. × 200.

Lymphosarcoma.—This is a round-celled sarcoma, in which the matrix has developed into a more or less perfect reticulum, like that of lymphoid tissue (Fig. 53). It may begin in lymphatic glands, or in connective tissue anywhere, and is a common form of mediastinal growth. It is distinguished from lymphadenoma by its more rapid course, by the formation of secondary growths by embolism, and by the absence, when the lymphatic glands are involved, of the typical distribution of follicles and stroma. Occasionally the growth is slower and the reticulum more developed (Fig. 54).

Alveolar Sarcoma.—This is a somewhat rare form of round-celled sarcoma which was first described by Billroth. The cells, which are large, sharply defined, and round or oval in shape, contain round, prominent nuclei, and are separated from each other by a more or less marked fibrous stroma. In some parts this stroma forms small alveoli within which the cells are grouped, but careful examination will always show that in most parts of the section the stroma really penetrates between the individual cells. This last-named character, together with the nature of the tissue from which they arise, serves to distinguish these tumors from the cancers, with which, in many cases, they may easily be confounded. The accompanying drawing shows their microscopic characters (Fig. 55). The stroma is often much more delicate, and the cell-masses are occasionally much larger than in the drawing. The cells are generally in close connection with the stroma, though vessels never pass in among them. In this latter respect they resemble epithelial growths. Ziegler considers that the alveolar structure may be due to the transformation of normal intervascular tissue into sarcoma-cells, while the vessels with the neighboring connective tissue remain as septa.

Fig. 55.

Alveolar sarcoma. From a tumor of the skin. × 200.

Alveolar sarcomata are met with principally in the skin, bones, and muscles. In the skin, where they are often multiple, they lead to ulceration. They tend to recur locally, and also to reproduce themselves in internal organs. Many alveolar sarcomata would now be placed under the heading "endotheliomata," as they appear to arise from endothelial cells.

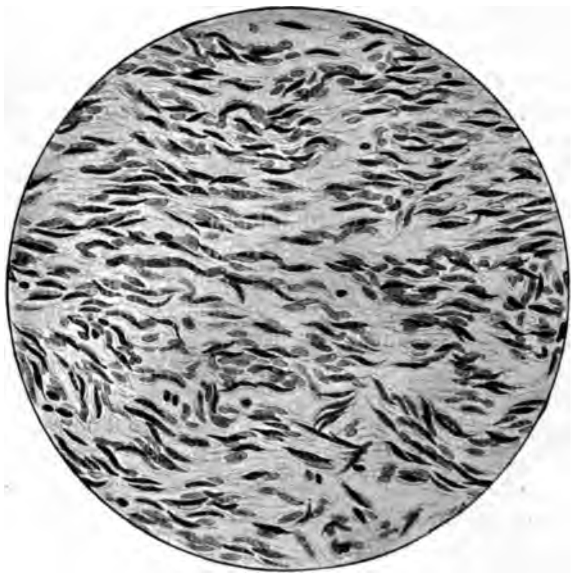
Spindle-celled Sarcomata.

These tumors are the most common of all sarcomata. They consist of cells, mainly spindle-shaped and fusiform, separated by only a little homogeneous or slightly fibrillated intercellular substance (Fig. 56), and often forming whorls around the vessels. The cells contain well-marked oval nuclei, with one or more nucleoli. They are arranged in bundles which pass in all directions through the growth, and often give it the appearance of a fibroma or myoma. In those portions of the section in which the bundles of spindle-elements have been cut transversely or obliquely, they present the appearance of round or oval cells. The cells vary considerably in size in different tumors, hence the division into **small** and **large** spindle-celled growths.

Small Spindle-celled Sarcoma.—In these the cells are small, often not more than $\frac{1}{1500}$ inch in length, and the intercellular substance is occasionally imperfectly fibrillated (Fig. 57). These growths are therefore somewhat similar to fibromata, and histologically they must

be regarded as occupying an intermediate place between embryonic and fully developed connective tissue. They grow from periosteum, fasciæ, and connective tissue in other parts. They are usually firm

FIG. 56.



Spindle-celled sarcoma. × 200.

and whitish or pinkish-white, and present on section a translucent somewhat fibrillated appearance. They are much more frequently encapsuled than any other variety of sarcoma, but they are very liable to infiltrate the surrounding structures, and to recur locally after removal.

FIG. 57.

Small spindle-celled sarcoma. From a tumor of the leg. × 200.

Large Spindle-celled Sarcoma.—The cells in these tumors are not only larger than in the preceding, they are also plumper, and both nuclei and nucleoli are especially prominent and frequently multiple (Fig. 58). The intercellular substance is more scanty, and there is a complete absence of any fibrillation. These growths are much softer in consistence than the small-celled variety. They are of a pinkish-white color, and are often stained by extravasations of blood, and in parts are sometimes almost diffluent from extensive fatty degeneration. They grow rapidly, and are usually exceedingly malignant. They occasionally give rise to blood-cysts.

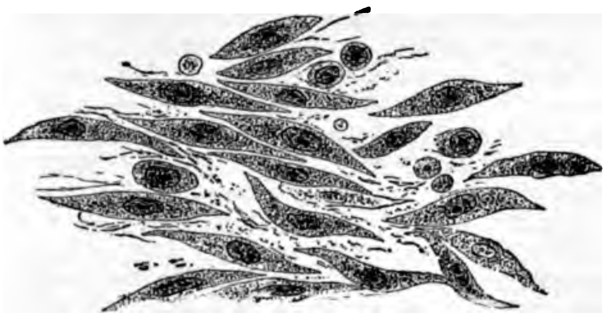
Melanotic Sarcoma.—This is a variety of sarcoma in which many of the cells contain granules of melanin[1] (p. 81), quite distinct from the

[1] Greek μέλας, black.

pigment of extravasated blood. The greater number of melanotic tumors are probably sarcomata.

Melanotic sarcomata originate principally in two situations—in the pigmented tissues of the eye and in the superficial integuments. In

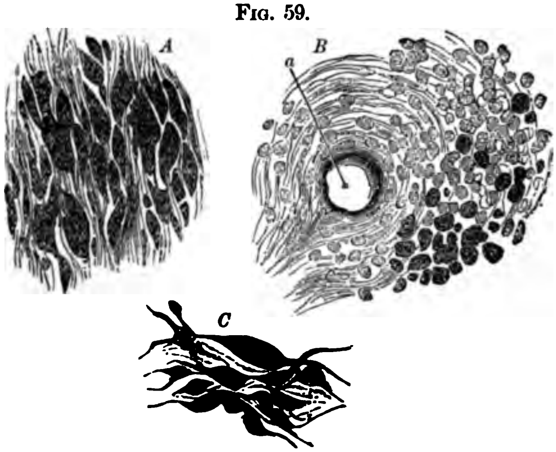
FIG. 58.



Large spindle-celled sarcoma. × 400.

both these situations pigment is a normal constituent of the tissues, and this tendency of pigmented structures to give origin to melanotic growths is exceedingly characteristic. These tumors usually consist of spindle-shaped cells (Fig. 59), and hence they are described in the

FIG. 59.



A melanotic sarcoma of the penis. *A*. Section showing the general arrangement of the elements. × 200. *B*. Section from the peripheral part of the growth, showing the "indifferent cells," amongst which are small isolated pigmented elements. At *a*, a bloodvessel is seen. × 200. *C*. Some of the elements separated by teasing. In these the pigment-granules are well seen. × 400.

present section; but in some cases the prevailing type of cell is round or oval. The pigment, which gives to them their distinctive character, consists of granules of a brownish or dark sepia color. These are mainly distributed within the cells (Fig. 59, *C*), but are also found

in the intercellular substance; in the latter position the pigment is not improbably derived from broken-down cells of the tumor. Frequently, only a very small proportion of the cells is pigmented, whilst in other instances the pigmentation is much more universal. In all cases, a large number of the elements will be found to be quite free from pigment.

These melanotic tumors are among the most malignant of the sarcomatous growths. Although they show comparatively little tendency to extend locally, they are rapidly disseminated by means of the blood-vessels, and occasionally also by the lymphatics: they thus reproduce themselves, often very rapidly, in distant tissues. Although the secondary growths almost invariably maintain their melanotic character, the degree of their pigmentation varies considerably. Whilst many of them may be perfectly black in color, others may be much paler—perhaps only streaked with pigment. The secondary growths are soft, usually distinctly circumscribed, and often encapsuled. They may occur in almost every organ of the body—the liver, the spleen, the kidneys, the lungs, the heart, the brain and spinal cord, and also the lymphatic glands and subcutaneous tissue, may all be simultaneously involved. When occurring in internal organs, the pigmentation is not always limited to the secondary nodules, but many of the cells proper to the organ itself are filled with granules of similar pigment, which is most abundant in the cells immediately adjacent to the new-growths. This pigmentation of the cells of the organ often extends for some distance beyond the confines of the tumor. Melanin or its chromogen is generally present in the urine.

Chloroma.[1]—The name chloroma has been applied to a very rare form of tumor, closely resembling lymphosarcoma histologically, but distinguished by its peculiar green color. The nature of the pigment is unknown; it rapidly fades on exposure to air. The growths originate in connection with bone, especially with the bones of the face. The disease has some apparent relation to leucocythæmia, the blood presenting marked lymphocytosis. (See Leucocythæmia.)

Osteosarcoma.—This is a variety of sarcoma in which the growth (usually spindle-celled) is either more or less calcified, or partially converted into true bone. As a primary growth it is met with almost exclusively in connection with bone, growing either from the periosteum or the medulla; but the osteoid characters are usually reproduced in secondary tumors occurring in the lungs and other parts.

Calcification is much more common than true *ossification*. Each of these processes may occur separately, but they are often combined. Bands and patches of granular appearance, in which the outlines of cells may still be visible, or in which all structure has disappeared, and which stain but slightly, show where calcification has occurred (Fig. 60). In other parts, especially near the bone, spicules having the structure

[1] Greek χλωρός, green.

of more or less perfect bone—Haversian canals, lacunæ, and imperfect canaliculi—will be seen penetrating the growth (Fig. 61). The spicules

FIG. 60.

Calcifying sarcoma. From a secondary tumor of the lung. Showing the calcification of a spindle-celled growth. × 200.

are generally vertical to the surface of the bone. In some cases a skeleton of bony spines radiates from the bone through the growth.

Both calcification and ossification may be very complete, but *a thin*

FIG. 61.

Ossifying sarcoma of lower jaw. *s*, sarcoma-tissue; *b*, new bone, growing from jaw, of which the structure is fairly typical; *p*, point of commencing ossification. Only nuclei of cells are indicated; close to the bone the stroma is very fibrous. × 40. (Boyd.)

margin of sarcoma-tissue is always present. This distinguishes the growth from a simple osteoma which has cartilage or periosteum on its surface, and is of much slower growth.

Myeloid Sarcoma.

These sarcomata, also known as *myeloid tumors* or *myelomata*, are allied to the spindle-celled sarcomata. They possess, however, certain histological peculiarities which probably depend upon the characters of the tissue from which they grow. They contain many of the large mul-

tinucleated cells, known as "myeloid cells"—which resemble the cells of the medulla of bone in a state of excessive nutritive activity—together with numerous fusiform cells like those met with in the spindle-celled varieties. There are also some smaller round and oval elements.

Fig. 62.

Myeloid sarcoma of the jaw. *a*, *a'*, *a''*, myeloid cells; *b*, *b*, spindle-cells cut transversely; *c*, *c*, spindle-cells cut obliquely; *d*, *d*, spindle-cells. × 400.

The large myeloid cells which give to these tumors their distinctive characters are usually much more numerous in those growths which originate in the medullary cavity than in those which spring from the periosteum. These various forms of cells are almost in contact, there being very little intercellular substance (Fig. 62). The growths are sometimes so vascular as to give rise to distinct pulsation. They often contain cysts.

Myeloid tumors almost always grow in connection with bone, the ends of the long bones being their favorite seat: they most frequently originate in the medullary cavity of the long bones. They are also frequently met with springing from the periosteum of the upper and lower alveolar processes, where they constitute one form of *epulis*.[1] When originating within the medullary cavity, the compact tissue of the bone becomes "expanded" over them, and they thus often communicate to the fingers, during examination, the peculiar sensation known to surgeons as "eggshell crackling." True expansion of bone is, of course, impossible; really, the old bone is absorbed from within by the tumor, and the periosteum lays down new bone on the surface; absorption is more rapid than new formation, and the thin surface layer of bone yields and crackles under pressure, or is actually wanting at

[1] Greek ἐπὶ, upon; οὖλον, the gum.

spots where pulsation is marked. Myeloid tumors may also originate in tendon-sheaths and synovial membranes.

These tumors are for the most part of firmer consistence than the other varieties of sarcoma. Many of them are firm and fleshy; others are softer, more resembling gelatin-size. They are not pulpy and grumous like the soft sarcomata, neither do they present the fasciculated appearance of the spindle-celled varieties. Their cut surface has a uniform succulent appearance, often mottled with patches of red. This red-brown or maroon color varies with the number of giant-cells present, and is very characteristic. The tumors are often encapsuled by the periosteal covering of the bone from which they grow. They are rare after middle life, and very rarely give rise to secondary growths. They are the least malignant of all sarcomata, and by some authorities are classed among the innocent growths as tumors of the medulla of bone, or *myelomata*.

When occurring in other connective tissues, these sarcomata are generally found where congenital defects are common; and the myeloid cells and even cartilage (Waring), which they may then contain, are, therefore, probably due to the inclusion of some misplaced rudiment.

Small **multiple myeloid sarcomata** are occasionally found as primary tumors in bone and other connective tissues. In bone, the tumors grow from the medulla, invade the bony tissue, and expand the periosteum. The affected bones soften, and in their subsequent changes simulate the condition met with in osteomalacia. In these cases albumose is often present in the urine. These tumors are more malignant than the single myeloid sarcomata previously described.

Angiosarcoma.

Angiosarcomata are round-celled, or less commonly spindle-celled, growths in which the vessels are so numerous and so large that in many cases the tumor appears to be made up of islets of sarcoma-cells surrounded by a single layer of flattened spindle-cells, and separated from one another by larger or smaller spaces containing blood.

Perithelial Sarcoma.

Perithelial sarcomata are growths consisting of parallel columns or globes (*cylindroma*), each of which is composed of a large central capillary vessel and three or four concentric layers of cells, probably derived from the adventitia of the central vessel. These columns are connected by myxomatous or sarcomatous tissue. The cells forming the columns often undergo mucoid changes. Ziegler, to emphasize the large size and number of the vessels and the general character of the tissue around them, has suggested the name *angiosarcoma myxomatodes*.

Endothelioma.

Endotheliomata are growths sometimes found arising from the endothelial lining of serous membranes, and consisting of large oval or angular cells contained in well-defined alveoli. These tumors are very similar in structure to carcinomata; but parts of the growth may show multiplication of pre-existing endothelial cells, and other parts may consist of spindle-cells and transitional forms.

PAPILLOMA.

Papillomata are new formations resembling in **structure** enlarged papillæ.

They consist of a basis of connective tissue which sends toward the surface numerous papillary processes, each supporting bloodvessels which end in a capillary network or single loop, the whole being enveloped in a covering of epithelium. The papillæ may be short and simple, as in an ordinary *wart* (Fig. 63); or they may be long, delicate, branching—giving off secondary and tertiary offsets—and very numerous, as in *villous tumors*. The covering epithelium in skin-growths is thick, hard, and stratified, and may actually bind the papillæ into a solid mass; but

FIG. 63.

Section of wart on skin. *a*, epithelium; *b*, connective tissue, continuous with epidermis and cutis respectively. × 18.

on mucous membranes the slender vascular processes are covered by a small amount of delicate epithelium, and in consequence they are easily lacerable (Fig. 64). Papillomata on serous membranes may be covered by a single layer of endothelial cells.

Hemorrhage and *ulceration* resulting from injury can hardly be classed as **secondary changes.** The only important change is the possible *conversion of a papilloma into an epithelioma.* In a wart all the epithelium is *on the surface,* no matter how irregular that surface may be. As soon as the epithelium begins to *invade the tissues beneath it,* the

FIG. 64.

A single small papilla from the villous papilloma of bladder shown on page 150. The epithelial covering has been accidentally separated in three places from the central structure. × 150.

Endothelioma.

wart has become a cancer. Pigmented warts not uncommonly form on the face in old age, and, especially if frequently irritated, may become epitheliomatous.

Four **varieties** can be readily distinguished:

1. The **ordinary skin-wart** with its covering of hard squamous epidermis. Condylomata and venereal warts, due to the irritation of the secretions of soft sores or gonorrhœa, deserve special mention. These,

though covered by squamous epithelium, are much softer, more vascular, and more luxuriant in growth than the ordinary skin-wart. They affect warm, moist parts.

2. The **soft warts** and **villous tumors** of all mucous surfaces. These are usually characterized by long delicate compound papillæ. The tongue,

Fig. 65.

Villous tumor of bladder. *a*, *a*¹, *a*², papillæ, *b*, normal mucous membrane. Reduced ⅓

cheek, larynx, and bladder are the parts most often affected. The papillary enlargements of the synovial villi, which are common in chronic arthritis, may be included in this group.

3. **Corns.**—These *commence* as papillomata; but, as the epidermis thickens and is pressed by the boot into the soft parts, the papillæ ultimately atrophy.

4. **Horns** some inches long occasionally spring from the skin. These consist of epithelium and sebaceous secretion, and originate from sebaceous follicles or from a sebaceous cyst. It is said that long papillæ project into their bases, so that they seem to be allied to warts. The base must be removed with the horn, or the latter will recur.

To the **naked eye,** the ordinary wart is a hard, abruptly elevated little mass, apparently formed of epithelium. It presents an irregular ("warty") surface, often divided by deep fissures (Fig. 63). If the investing epithelium be abundant, or the papillæ be very short, a rounded mass, having a merely furrowed surface, results; but as the papillæ lengthen and the epithelium thins, the growth presents first a cauliflower, then a branched, and finally a villous appearance. The latter appearance is best seen on placing a "villous tumor" of the bladder in water, when the long delicate papillæ float up (Fig. 65).

They are evceedingly vascular. If a section of a papilloma be made, the relation between stroma and epithelium, above described, can be seen, even with the naked eye (Fig. 63).

FIG. 66.

Duct-papilloma of breast from one of the larger ducts of the breast. The new-growth, which consists of a fibrous stroma penetrated by channels lined with a single layer of epithelium. has nowhere extended beneath the surface of the lumen of the duct it distends, and from which it grows. $\times$ 20. (Specimen by Dr. Rolleston.)

Papillomata **originate** from *skin*, from *mucous*, *serous*, and *synovial membranes*, and from the *ducts of glands* (Fig. 66). They most frequently grow from pre-existing papillæ; sometimes, however, they occur where no papillæ exist, springing directly from the subepithelial connective tissue: this is the case in the stomach and larynx. As all new growths on free surfaces tend to become "papillary," this form of tumor is probably the result of physical conditions. According to

this view, a wart is simply a fibroma become papillary by an accident of position, and papillomata as a class should therefore disappear. Many papillomata are rather inflammatory overgrowths than true tumors.

Clinically, warts, so long as they remain warts, are quite innocent. They are common in childhood and early adult age, especially upon the hands and face. They may be single, but upon the hands they are commonly multiple. When not congenital they generally disappear after a time, though they may persist for years. Papillomata on mucous surfaces give trouble, and may cause death by bleeding: in the bladder, difficulty may arise from obstruction to the inflow or outflow of urine, the entrance of the ureter being a favorite seat. Lastly, the tendency of warts and warty surfaces (*e. g.*, *ichthyosis linguæ*) to become epitheliomatous in advanced life must be remembered.

ADENOMA.[1]

Adenomata—or, as they are sometimes called, **glandular tumors**—are new formations of epithelial gland-tissue, more or less resembling, but distinct from, the glandular tissue of the organs in which the tumors arise. The new-growths are incapable of performing the function of the tissue they imitate, and their ducts do not enter those of the gland.

In **structure** adenomata consist of numerous tubules or acini, according to the gland in which the growth arises. These tubules or acini are generally lined with a single layer of epithelial cells, though there may be two or three layers. A section cut very obliquely through the wall of one of these acini will, by cutting across adjacent cells at different levels, give the appearance of several superimposed layers. The acini communicate with each other and are grouped together, being separated merely by connective tissue in which are contained the bloodvessels. The connective tissue varies in amount; when it is much in excess of the normal, the growth is called an *adenofibroma*. Sometimes, in the most rapidly growing forms, the stroma is richly cellular, consisting of round and spindle-cells; the histological distinction between such growths and sarcomata is impossible (Fig. 67).

All growths originating in glandular organs may be associated with more or less glandular structure. In the mamma, for example, sarcoma, myxoma, and other forms of tumor, are often so intermingled with the gland-tissue of the organ that it becomes difficult to say which is the predominant structure. In many cases it is evident that the development of such tumors is accompanied by an increase of the gland-tissue among which they grow. Mixed forms are thus produced—*adenosarcoma*, *adenomyxoma*, etc. Adenoma is, by itself, an insufficient name for these tumors, because their stroma is different from, or in excess of, that found in normal gland-tissue. In the uterus tumors are found consisting of glandular tubules embedded in muscular tissue, and have been called *adenomyomata*.

[1] Greek ἀδήν, a gland.

The most frequent **secondary change** found in these tumors is *fatty degeneration* of the epithelium, which may give rise to the formation of small caseous masses in the growth. Dilatation of the saccules and tubules into *cysts*, and *mucoid softening*, are also common. The origin of cancer has several times been traced to an adenoma.

Adenomata almost always **originate** from *pre-existing glands.* They generally grow slowly, and possibly, in many cases, from some hitherto quiescent, congenitally misplaced, rudiment; otherwise it is difficult to explain the complete encapsulation and separation from the normal gland which distinguishes an adenoma from a localized enlargement. The latter swelling remains in intimate relation with the gland, and is probably often of inflammatory origin.

FIG. 67.

Adenoma of mamma. *a*, fibrous tissue; *b*, acini lined with epithelium. × 250.

Adenomata are commonly met with in the following organs:

Mamma.—This is much the most common seat of adenoma, or rather of adenofibroma, for a glandular tumor which is structurally indistinguishable from normal breast-tissue is very rare (Fig. 68). The arrangement of the epithelium, the number and size of the spaces, the proportion of stroma, and the number of cells it contains, are more or

less abnormal (Fig. 68), hence the name "adenofibroma" is generally most applicable. They are encapsuled, and are round, oval, or lobulated, lying in or on the breast. They are of hard elastic consistence. The surface on section is slightly convex and not cupped, as in chronic cancer (*scirrhus*). It is either lobulated and fibrous-looking, or shows distinct slits and a racemose structure even to the naked eye. These tumors are most common in early life. They may be multiple.

FIG. 68.

Adenofibroma of mamma. Showing new-growth of gland-structure and of connective tissue. × 50.

Many adenofibromata contain cysts, which may be very numerous, and vary in size from slight dilatations of ducts and acini to cavities containing some ounces of yellow mucoid fluid, which may be reddish or brownish from extravasated blood. Many of these cysts are lined with cylindrical epithelium like that of the gland-spaces, but others appear to be formed by localized softenings of the stroma. At first they appear on section as irregular and branched fissures, then as spaces full of fluid; in other cases they are almost completely filled by papillary fibrous growths projecting inward from the wall and covered by cubical epithelium. These cystic growths are called *cystic adenomata;* or, if the stroma is richly cellular, *cystic adenosarcomata*. Papillary growths having an adenomatous structure may occur in the mammary ducts (Fig. 66). The non-cystic growths must be distinguished from local and general hypertrophies of the gland, and from chronic mastitis, in which the fibrous tissue is less localized and generally includes fat and atrophied acini.

Ovary.—Adenomata frequently arise in the ovaries. The acini of the growth are derived from ingrowths of the germinal epithelium of the surface of the ovary, while the fibrous or myxomatous septa

take their origin from the stroma. Of the original acini the largest number remain little more than microscopic in size; some, however, enlarge considerably, and into the cavities of many of these, compound papillary ingrowths occur (Fig. 69), consisting of a framework of

Fig. 69.

Papillary growth inside an ovarian cyst, projecting from its wall (*w*). It consists of loose connective tissue (*c*), containing many branched cells, covered by a layer of columnar cells (*e*); secondary processes are numerous (*p*). × 20. (Boyd.)

stroma and a covering of columnar cells; while a still smaller number of acini enlarge enormously, and together form the well-known large compound multilocular cysts of the ovary. The contents are clear or turbid, mucoid or gelatinous. The tumors are as a rule innocent, but if carcinomatous or sarcomatous developments occur in their interior, they rapidly assume malignant characters.

Kidney.—The kidneys are the occasional seats of growths somewhat resembling those of the ovary, and tumors apparently derived from misplaced cells of the suprarenal body (*hypernephromata*) also occur in these organs.

Prostate.—In advanced age some of the tumors which form in this body contain glandular tissue as well as muscle and connective tissue (*adenomyoma*).

Thyroid.—Apart from the hypertrophy of this gland occurring in endemic goître and Graves's disease, distinct encapsuled tumors having the structure of the normal thyroid may rarely be found.

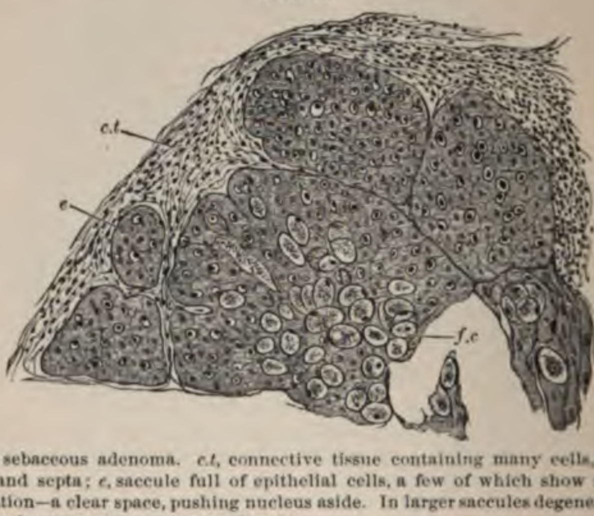
Parotid.—Pure glandular tumors are infrequent, and the gland-epithelium of such tumors as do occur is generally very atypical. Fibroadenomata are commoner, but the *ordinary "parotid tumor"* is

a mixed growth containing cartilaginous, myxomatous, and other tissues. The other salivary glands are still less frequently affected.

Liver.—Small encapsuled tumors having the structure of the liver have been described. The so-called "multiple adenomata" of the liver, associated with cirrhosis, appear to be simply masses of hepatic cells cut off by septa of newly formed fibrous tissue. The occasional origin of primary cancer in such livers supports the hypothesis suggested to explain the origin of tumors.

Uterus.—The adenomyomata occurring in the uterus contain true glandular tissue.

FIG. 70.



Lobule of a sebaceous adenoma. *c.t*, connective tissue containing many cells, and forming capsule and septa; *e*, saccule full of epithelial cells, a few of which show signs of fatty degeneration—a clear space, pushing nucleus aside. In larger saccules degeneration is more general and extreme (*f.c.*). × 200. (Boyd.)

Glands of Mucous Membranes.—Gland-tissue enters largely into the structure of some of the "mucous polypi," which may spring from any mucous membrane, especially as a result of catarrh. In some cases it is probable that the glands primarily enlarge, then project, and finally become polypoid. In other cases it is supposed that localized increase of connective tissue from inflammation may lead to increase of the epithelial structures in relation with it. Polypi of the nose, stomach, intestines, rectum, and uterus are examples. The connective tissue is soft and œdematous; the surface is covered by the epithelium of the part.

Sebaceous and Sweat-glands.—So-called adenomata of these glands are uniform enlargements rather than tumors. Fig. 70 shows a small portion of a sebaceous "adenoma" from the chin of a child.

Among **secondary changes** are *calcification*, which may affect the epithelial masses, and *ossification*, which may take place in the fibrous stroma. Tumors undergoing the latter change are rare, and have been called "osteomata of the skin" (p. 115).

Clinically, adenomata and adenofibromata are almost invariably innocent. They may, however, occasionally become malignant. A few

cases occur which clinically and microscopically appear to be ordinary adenomata, but which *recur locally* after removal. There are also cases on record of the *generalization* of ovarian adenomata as well as of tumors having the structure of the normal thyroid gland.

The lumina of racemose adenomata are sometimes filled up with epithelial cells; it is then impossible to distinguish them microscopically from carcinoma in its earliest stage—that of multiplication of epithelium—unless the mass has penetrated the muscularis mucosæ, when its malignant nature is assured. The occasional origin of cancer from adenomata has been proved, both microscopically and clinically.

As there is no exact line of division between sarcoma-tissue and fibrous tissue, it is often impossible to say with certainty which name—*adenofibroma* or *adenosarcoma*—should be applied to a given tumor containing gland-tissue.

CARCINOMA.[1]

Carcinomata or cancers are tumors consisting of epithelial cells lying in a network of connective tissue (*stroma*).

Origin.—It is now generally believed that epithelial cells can originate only in cells of the same type; it is, therefore, only from such cells that carcinomata can spring. They may arise equally in epithelium derived from the *epiblast*, forming the skin and its appendages, the mammæ and other glands; or from the *hypoblast*, which lines the alimentary canal and gives origin to the great glandular viscera connected with it. Cases have been recorded of primary cancer in lymphatic glands, in bone, in the membranes of the brain, and in other places where no true epithelium exists. Of such cases various explanations are possible. (1) Some small primary growth may exist which is overlooked owing to its giving rise to no symptoms, the tumor, which is apparently primary, being really derived from this by metastasis. (2) Some abnormality may have existed, such as a detached piece of mammary tissue lying near the axillary glands, or the fœtal inclusion of an epithelial rudiment (p. 95). (3) There are certain kinds of connective-tissue cells, such as the endothelium of bloodvessels and serous membranes, which are indistinguishable from epithelium and which give rise to tumors morphologically identical with epithelial growths (*endotheliomata*, p. 128). Some other sarcomata (*alveolar sarcoma*, *cylindroma*) also resemble carcinomata so closely that mistakes in diagnosis may reasonably occur. (4) If the theory of new growths suggested on page 99 is tenable, it appears possible that a true epithelial growth may originate in any spot, from the lodgement of a mass of epithelial cells displaced from their normal connections and carried thither by the lymph- or blood-stream.

Epithelial cells are said to occur around cancers lying in the connective-tissue spaces isolated from the growth itself. This cannot, however, be used as an argument in favor of the development of such cells from connective tissue, since cancer-cells are undoubtedly carried

[1] Greek καρκίνος; Latin *cancer*, a crab.

away by the lymph-stream even to distant parts of the body. Often delicate chains of cells one or two inches in length have been traced between a main growth and an apparently isolated nodule. Such a chain might easily be interrupted and cells thus left isolated. It is worthy of note that very few cases of so-called primary mesoblastic cancer have been reported since microscopical examinations have become more exact.

When conditions are favorable, and a cancer originates either in the growth of a resting embryonic rudiment (Cohnheim) or from displaced epithelial cells, it tends to grow through any basement-membrane that may exist, and spread along lymph-spaces and channels in the connective tissue. Epithelial cells thus lie in the lymph-current, where they are bathed in nutrient fluid and are able to multiply rapidly (p. 100). Glandular infection is in this way readily produced. The shape and arrangement of the growing cell-columns depend upon the resistance met with in their progress; when resistance is great, the columns are narrow; when it is slight, they widen out.

The stroma of the growth is, at first, formed by the normal connective-tissue bundles of the part; but, as the tumor enlarges, irritation of the surrounding parts is set up, round-celled infiltration occurs at the advancing edge of the growth, and fresh fibrous tissue is formed by multiplication of the connective-tissue cells. At first, other elements of the part may persist in the stroma (*e.g.*, fat-cells in the breast and muscle-fibres in the prostate), but such enclosed cells rapidly disappear as the tumor advances.

Growing in this way carcinomata are scarcely ever encapsuled. In a few rare instances, tumors having the structure of epitheliomata may be met with (*e.g.*, in the soft palate) surrounded by a definite capsule. In almost all cases, however, cancers rapidly infiltrate surrounding structures. In many cases, a zone of small-celled infiltration may be seen for some distance beyond the borders of the tumor, so that there is no line of demarcation between it and normal tissues.

Structure.—It has already been stated that carcinomata consist of epithelial cells and connective-tissue stroma. The **cells** are characterized by their large size, by the variety of their forms, and by the magnitude and prominence of their nuclei and nucleoli (Fig. 71). They are round, oval, fusiform, caudate or polygonal—exhibiting, in short, every diversity of outline. These variations in form are principally owing to the mutual pressure to which the cells are subjected in their growth. The nuclei are large and prominent, round or oval in shape, and contain one or more bright nucleoli. The nuclei are most frequently single, but two are often met with, and in the softer and more rapidly growing cancers there may be more. The cells lie in the alveoli in more or less close contact one with another: *no stroma passes between them.* They rapidly undergo degenerative changes. Many cells may be seen to contain

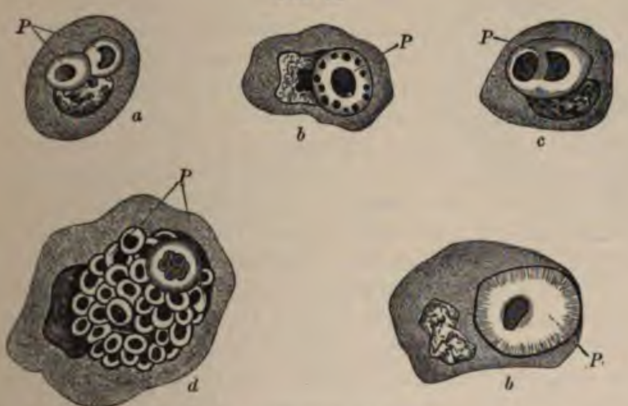
FIG. 71.

Cells from a scirrhus of the mamma. ×350.

molecular fat, and in the central portions of the alveoli so many cells may be destroyed that the growth may at places be represented by mere amorphous débris, containing here and there the free nuclei of those which have perished. Cells exactly similar to cancer-cells are met with in other morbid growths and in the normal epithelia: there is thus no distinguishing characteristic of cancer-cells.

In recent years the minute structure of carcinomata has been subjected to a very rigid examination in search of any parasite that may be present. It is generally admitted that, when suitable portions of cancerous tissues are hardened and stained by special methods, peculiar appearances are to be seen, the exact significance of which is still in dispute. These are known as *cancer-bodies* or cell-enclosures. They vary greatly in size, being on an average somewhat smaller than red corpuscles. They are for the most part spheroidal in form, and have a sharply defined outline. They possess staining affinities somewhat different from those of the ordinary cells of the growth. Their substance is usually homogeneous, but occasionally mottled or granular. At or near to the centre is a small deeply stained part which has been supposed to represent the nucleus or nucleolus. It is usually single, round or oval in shape, and there may be a faint radial striation visible between it and the periphery (Fig. 72). The number of cancer-bodies,

FIG. 72



(*a*) Two complete cancer-bodies in a single cell. × 600.
(*b*) Cancer-body showing granules at the periphery of the cell. × 600.
(*c*) Cancer-body with a dividing nucleus; the connecting threads are shown. × 600.
(*d*) Cell containing a cluster of small cancer-bodies. × 1000.
(*e*) Cancer-cell from scirrhus of breast. Faint rays are seen at periphery of parasite. × 1200.
(*P*) Cancer-body or supposed parasite.
(Specimens and drawings by Ruffer.)

or fragments of such, occurring in cells is said to be generally even, and this has been interpreted as being the result of a process of multiplication by binary division. Spore-formation has been said to occur by some observers, but is not generally admitted. Cancer-bodies are

usually found enclosed within the cells of the growth, but they have also been described lying in the alveolar spaces outside the cells, and even in the lymphatics of the alveolar walls. Their position has no ascertainable influence on their general characters. The cancer-body may occupy only an insignificant part of the cell, or may fill nearly the whole of it and displace the nucleus to the periphery. Still more rarely these bodies may be found, singly or in numbers, within the nucleus itself; in this case they are generally smaller than when found elsewhere.

The cancer-bodies are most common in growing edges of tumors and in secondary deposits, and are rarely, if ever, found in degenerated parts. On the other hand, there is no evidence that they excite any unusual activity of growth in the cells containing them; indeed, it appears somewhat rare to find signs of nuclear division in such cells. As degeneration occurs the bodies lose their sharp contour; and Ruffer has drawn attention to the fact that this not infrequently happens when a leucocyte invades a cell already occupied by a cancer-body.

The nature of these bodies is not as yet definitely ascertained. Soon after attention was first directed to them it was suggested that they were parasitic *protozoa*. Ruffer pointed out a resemblance to the protozoa of malaria (see Malaria), in which the "rosette-stage" is similar to an appearance which he met with in cancer-bodies. The occurrence in rabbits of a disease of which the morbid anatomy is somewhat analogous to tumor-formation, and which has been proved to be due to a minute organism of the class *Sporozoa*, lent additional weight to this view. Schaudinn, however, examined many specimens of cancer containing these bodies, and was unable to find any which he could regard as protozoa. Other observers (Roncali, Plimmer) have identified the cancer-bodies with parasitic *fungi*. Plimmer, indeed, succeeded in isolating and cultivating (anaërobically) certain fungi from cancers, which he considers may possibly be found to belong to the saccharomycetes. He finds that, when certain animals are inoculated intraperitoneally with the cultures, death results, with the production of endothelial tumors; and that cultures from these growths will, under similar conditions, produce similar results.

It is not yet satisfactorily proved, however, that parasites of any kind are constantly present. Many bodies which have been looked upon as parasitic in cancers undoubtedly admit of simpler explanation. Thus it is maintained that many of these so-called parasites are nothing more than the appearance produced by the invagination of a part of one cell into the substance of another, the section being made through both cells parallel to and just below the surface through which the imbedded cell enters. Other cancer-bodies may be merely leucocytes enclosed within the cells of the growth. Another suggestion is that these bodies are due to endogenous formation of new cells from those of the original growth. This may either occur from an arrest of the process of direct division (*amitotic*) or from some irregularity in that of indirect division (*mitotic, karyokinetic*). Instances of such irregular

karyokinesis may be seen at times in cancer-cells, there being a tripolar or quadripolar arrangement of chromasomes instead of the usual bipolar figure. It is possible that round a detached portion of chromatin a cell may form and grow rapidly, but may yet remain a daughter-cell within the substance of its parent. If, however, this be the case, it is difficult to see why the daughter and parent cells should present any marked differences from one another in their staining-reactions. The most probable explanation of many of the unusual appearances seen in cancer-cells is that they are due to different forms of degeneration of the cell-protoplasm. Epithelial cells are liable to changes whereby various substances are formed in them (keratin, hyaline, colloid), and all new growths are specially subject to retrogressive changes in their constituent cells. The special forms of nuclear division which are found in cancer have been alluded to previously.

The **stroma** present in carcinomata varies considerably in amount, being much more abundant in some specimens than in others. It consists of a more or less distinctly fibrillated tissue, arranged so as to form alveoli of varying size and shape, within which the cells are grouped. It is not closely connected with the cells and does not penetrate between them. The alveoli communicate with one another so as to form a continuous cavernous system (Fig. 73). The characters of the stroma vary with the rate of growth of the tumor: if this is rapid, round and spindle-shaped cells will be present (Fig. 75); if, on the other hand, it is slow, the cells will be few and the tissue will be dense and more fibrous in character (Fig. 76). The latter is the condition in which it is most commonly met with.

FIG. 73.

The alveolar stroma from a scirrhus of the mamma. The cells have been removed by pencilling. × 200.

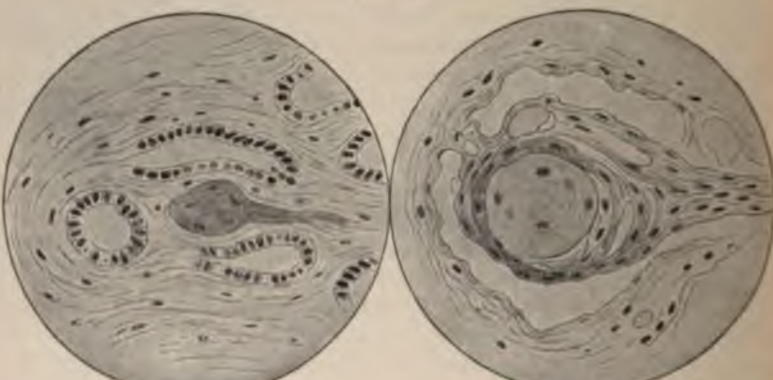
In the stroma are the **bloodvessels.** These are often very numerous and form a close network round the alveoli. They are limited to the stroma and never pass into the epithelial masses. This distribution of the bloodvessels is important, as it serves to distinguish carcinomata from sarcomata (p. 116). Alveolar sarcomata and endotheliomata, however, resemble carcinomata in this respect. The bloodvessels leading to a cancer, as to other tumors, are often greatly enlarged. The cause of this enlargement, and the mechanism by which it is brought about, are not well understood. **Lymphatic** channels communicate freely with the alveoli. This explains the great tendency of cancer to infect lymphatic glands. In fact, the alveoli of the growth may be regarded as dilated lymphatic spaces, along which the epithelial columns grow, following the lines of least resistance.

The **physical characters** of carcinomata are so diverse that they will be separately referred to when the different varieties are under consideration.

Varieties.—Just as normal epithelium presents several varieties,

squamous, columnar and cubical, so the tumors which spring from different epithelia are of different anatomical structure, inheriting, to a greater or less extent, the form and tendencies of the variety of epithelium from which they originate. Thus, cells of cancers springing from stratified epithelium tend also to undergo the same evolution, ending in cornification, and in many cases they show prickle-cells. Columnar epithelium often retains its typical arrangement and continues to surround open spaces; in other cases the cells may multipy so as to fill these spaces, the outermost layer of cells generally, however, retaining a cylindrical shape. Cells of acinous glands undergo no evolution (*e. g.*, horny change); by multiplication they produce cells of their own kind, which may be much altered in shape by mutual pressure. Upon this retention by the cells of ancestral anatomical characters is based the classification of carcinomata into *squamous-*, *columnar-*, and *spheroidal-celled* varieties. The squamous and columnar forms are often known as *epitheliomata*, owing to their resemblance to the structure of normal covering epithelium; but the cells of glands are equally epithelial in character, and no real distinction exists between glandular carcinoma and epithelioma. Indeed, ancestral peculiarities are not always retained. Thus, certain cancers springing from stratified epithelium—perhaps from the small glands in relation with it—undergo no horny change and are indistinguishable from spheroidal-celled cancer, and

Fig. 74.



Metaplasia of epithelium. From a carcinoma of the bile-duct. The figure on the left shows the original columnar-celled growth; that on the right shows a cell-nest, typical of squamous epithelioma, into which the growth became in places transformed.

tumors springing from columnar epithelium may in many parts present an exactly similar appearance, or may even in some cases (uterus; bile-duct) resemble squamous epithelioma, exhibiting formations like the cell-nests characteristic of the latter variety of tumors. (Fig. 74. See also Metaplasia.)

In all varieties of carcinoma the secondary growths tend to repeat the peculiarities of the primary tumor. The rate of growth and consequent proportion of stroma present may, however, vary; secondary

growths in internal organs often developing with great rapidity, and being softer and more vascular.

Secondary Changes.—The most important is *fatty degeneration.* This occurs in all the varieties of carcinoma. The more rapid the growth, the earlier does this retrogressive change take place. It produces softening of the growth, which is often reduced to a pulpy cream-like consistency. *Hemorrhage, pigmentation, mucoid* and *colloid degeneration* may also occur, leading to *cyst-formation.* Cysts may also be due to blocking of ducts, as, for example, in the mamma. *Calcification* and true *ossification* are very rarely met with. Formation of an *abscess* is rare, but important.

Clinical Characters.—Cancers occur with increasing frequency after the age of thirty-five: below that of thirty they are rare tumors. They occur in certain organs at an earlier period of life than in others, carcinoma of the mamma and cervix uteri being met with not infrequently in comparatively young subjects, while that of the lip or œsophagus generally arises in elderly persons. The uterus and mamma are the seat of carcinoma more frequently than any other organ, thus causing the female sex to present a slightly greater ratio of deaths from this disease than the male; but, apart from these organs, the incidence of the disease upon the two sexes is practically equal.

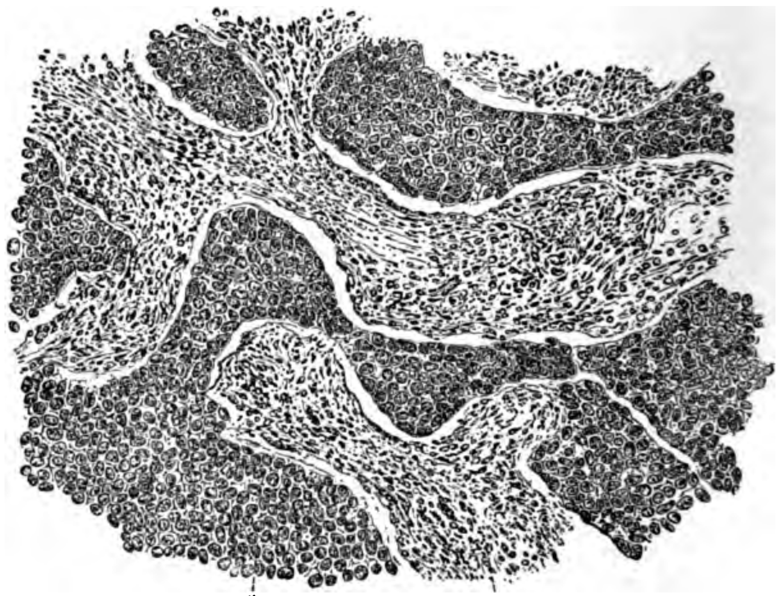
Primary carcinomata are almost always single. As a group they are among the most malignant tumors. They grow rapidly, widely infiltrate surrounding parts, largely infect lymphatic glands (p. 118), and ultimately become generally disseminated throughout the system. Unless excised very early and very freely, they recur *in loco.* They frequently break down and give rise to very offensive ulcers which bleed readily. The different types of carcinoma vary considerably in malignancy. As a rule, those forms of acinous cancer which exhibit a small relative amount of stroma and a richness in epithelial elements are the most speedily fatal. Colloid degeneration appears to diminish malignancy. Occasionally an encapsuled tumor is met with, especially in the soft palate, showing no sign of malignancy, yet having the structure of acinous cancer. In the variety known as "atrophic scirrhus" the duration of the disease is not uncommonly from ten to twenty years, and the extension only local and glandular.

Squamous epithelioma is clinically much the least malignant of the cancers. It extends locally, breaks down early, and often infects the neighboring lymphatic glands, but it comparatively rarely reproduces itself in internal organs. This is probably owing to the size and character of its epithelial elements, which renders them much less liable to transmission by the blood- and lymph-streams than the cells of the other varieties of cancer. Its malignancy varies curiously with its seat: thus, on the skin of the face, epithelioma has generally a very chronic course, and rarely affects the glands; on the lip, early excision gives a fair chance of cure; on the tongue, its course is often so rapid, infection of the glands so early, and cachexia and death so speedy, that it must be ranked as one of the most malignant tumors.

I. Spheroidal-celled or Acinous Carcinoma.

This is often divided into two separate varieties, according to the relative amount of stroma and cells, the harder growths, with much fibrous tissue and scanty epithelial cells, being known as *scirrhus*,[1] the softer kind, rich in cellular elements, being called *encephaloid* or medullary carcinoma. Encephaloid and scirrhus cannot, however, be

FIG. 75.



Scirrho-encephaloid of breast. *a*, cells; *b*, stroma. × 250.

regarded as in any way constituting distinct varieties of carcinoma. There are many intermediate stages between them (*common cancer*, *scirrho-encephaloid*, Fig. 75), and it may happen that the same tumor presents in one part the characters of scirrhus and in another or in secondary growths that of encephaloid cancer. The physiological prototype of this form of carcinoma may perhaps be seen in the solid columns of epithelial cells which are produced in the embryo to form the glandular viscera.

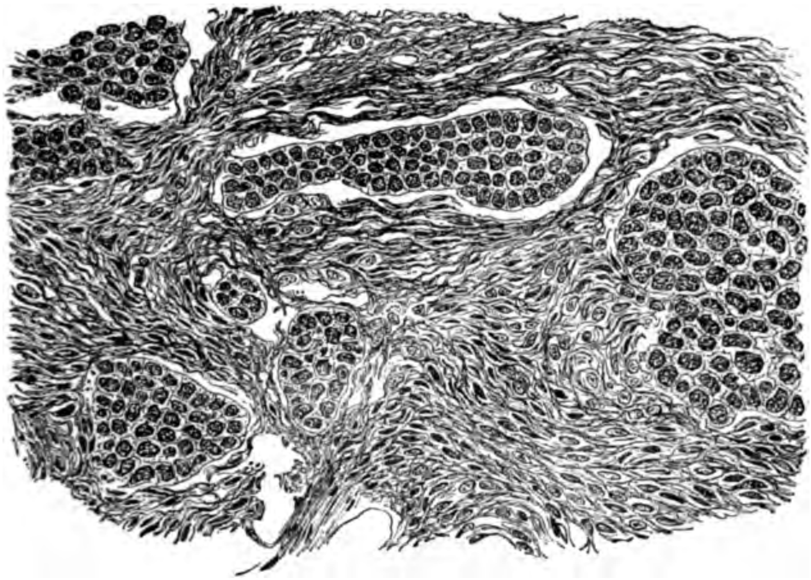
1. **Scirrhus** or **chronic cancer** is characterized by the amount and density of its stroma, and by the comparative slowness of its growth. The latter point probably accounts in great measure for the peculiarities of its structure and physical characters (Fig. 76).

The epithelial growth, although at first it may be luxuriant (Fig. 75), quickly subsides. The cells soon atrophy and undergo fatty degeneration. They are most abundant in the external portions of the tumor, where growth is taking place; in the central portions (Fig. 77) they are fewer, and may be almost entirely wanting.

[1] Greek σκιρρός, hard.

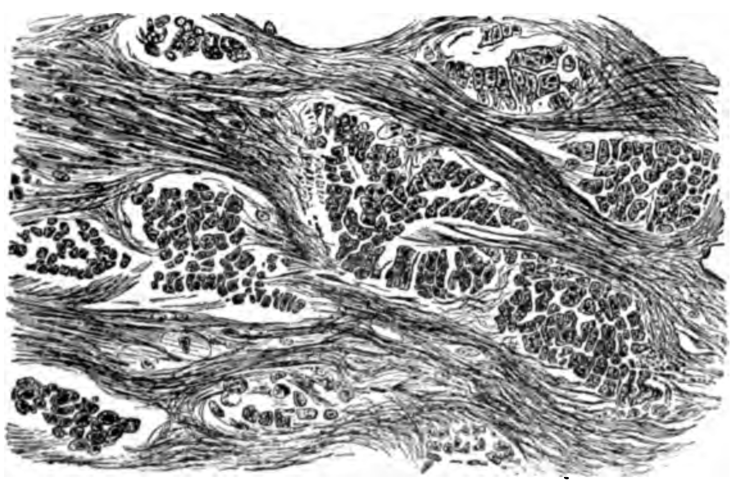
The *degeneration* of the epithelial elements is probably due to obliteration of the vessels by the scar-like contraction of the stroma,

FIG. 76.



Scirrhus of breast. From the circumference of a growth. × 250.

FIG. 77.



Scirrhus of breast. From the centre of same growth as Fig. 76. The cells are shrunken and degenerated and the stroma less cellular. × 250.

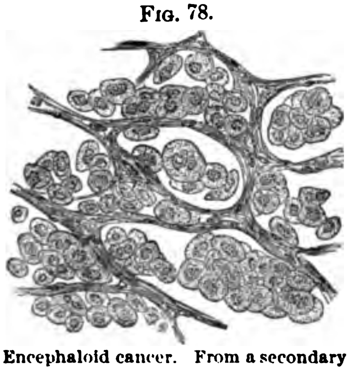
which quickly becomes hard and fibrous. In this way growth of that part of the cancer is arrested. The whole of the central portions may

thus ultimately consist of dense fibrous tissue, amongst which are scattered groups of atrophied epithelial cells and fatty débris (*atrophic scirrhus*); but even in these cases the epithelial structure is distinctly visible at the periphery. The amount of atrophy and contraction varies considerably in different cases.

The *physical characters* of scirrhus are due to the abundance of its stroma. The growth is firm and hard, and is usually depressed in the centre, owing to contraction of the fibrous tissue and atrophy of the cells. This contraction is very characteristic of scirrhus of the breast, where it causes retraction of the nipple and puckering of the skin. The growth is very hard, and creaks as it is cut. The surface of the section is generally "cupped," and of grayish-white, semi-translucent appearance, like that of an unripe pear. It is more or less mottled with dots and streaks of opaque yellow, due to fatty epithelium in alveoli or milk-ducts. The latter may be cystic. The central parts are pale and fibrous, the more external are pinker—because contraction has not obliterated the vessels—and less firm than the central portions of the growth. They yield, on scraping, a juice which is rich in nucleated cells, free nuclei, and granules. The outlying parts of the tumor can be brought into view by the local application of a 5 per cent. solution of nitric acid, the affected areas appearing as opaque white streaks.

By far the commonest seat of scirrhus is the female breast. It is also found in the male breast, the stomach, the liver, the pancreas, the prostate, the skin, and the mucous membranes, where it starts from racemose mucous glands. The secondary growths to which it gives rise are often encephaloid.

FIG. 78.



Encephaloid cancer. From a secondary cancer of the liver, showing the large size of the alveoli and the thinness of their walls. In the latter, a large number of connective tissue nuclei are visible. × 200.

2. Encephaloid or acute cancer differs from the preceding in the greater rapidity of its growth and in the consequently smaller amount of its stroma, and the greater softness of its consistency.

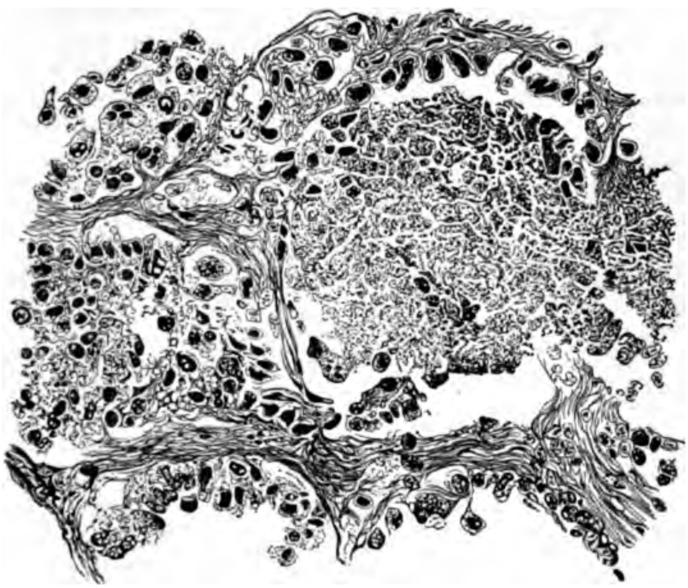
The epithelial growth is rapid and abundant; the cells, which may be either larger or smaller than those in scirrhus, quickly undergo fatty degeneration, so that often there are more free nuclei visible than cells (Fig. 79).

The proportion of stroma is very small, and, owing to the rapidity of its growth, it is much less fibrous than that of scirrhus, and does not undergo a similar cicatricial contraction (Fig. 78). The bloodvessels are often very abundant, and the tissue supporting them is soft and non-resistant. Hemorrhage into these growths is, therefore, frequent.

Encephaloid cancer is of a soft, brain-like consistency and appear-

ance (from which its name is derived), the central portions, where fatty degeneration is most advanced, often being completely diffluent. The tumor is sometimes more or less lobulated. On section, the undegenerated parts are pinkish-gray, soft, and translucent, while the degenerated form a white pulpy mass, which is often irregularly stained with extravasated blood.

FIG. 79.



Encephaloid cancer undergoing necrosis and fatty degeneration. The nuclei of some of the cells, especially those nearest the thin fibrous alveoli are stained, although their protoplasm has broken up and is not distinctly marked off from the alveolar walls. The outlines of a few of the rest are still visible, though their contents are granular and their nuclei unstained. The greater number have been converted into a mass of granular fatty débris. $\times$ 250.

Encephaloid is much less common than scirrhus. It is most frequently met with in internal organs as a *secondary* growth. It is sometimes *primary* in the testis and mamma. It may fungate and bleed (*fungus hæmatodes*). Many growths formerly described as encephaloid cancers were really soft sarcomata (see p. 120).

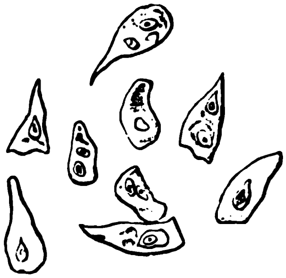
II. Squamous Epithelioma.

This constitutes a tolerably distinct variety of carcinoma, but transitional forms between it and scirrhus are occasionally met with. It always grows from a surface covered by squamous epithelium, either cutaneous or mucous (the junction of the two being a common seat). Its epithelial elements closely resemble those of squamous epithelium.

Many of the cells (Fig. 80) are considerably flattened and distorted

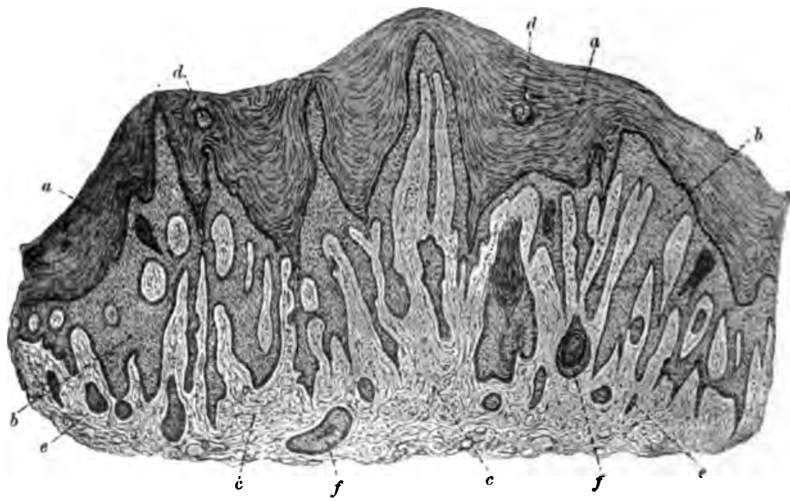
in shape, resembling those of the superficial layers of the epidermis; others are like those of the Malpighian layer. They grow down from the surface-epithelium into the lymph-spaces of the connective tissue, and, pushing their way along these, are formed into solid cylinders, which twist about, branch, and intercommunicate, swelling out at some points and becoming constricted or even interrupted at others (Fig. 81). Single epithelial cells may be recognized here and there, evidently swept on by the lymph-stream. The rods cut across appear as round or oval masses of cells, of which the outermost are usually large, while the central are more or less squamous and form a yellowish onion-like mass. Sometimes the central cells appear large and vesicular, while the outermost are scaly and flattened. These concentric masses of cells are called *concentric globes*, or *epithelial nests*, and, though not distinctive or essential, they are exceedingly characteristic of epithelioma (Fig. 74). The cells forming them are usually fatty and may be so closely

FIG. 80.



Cells from an epithelioma of the lip. × 250.

FIG. 81.



Squamous epithelioma. *a*, horny epithelial layer; *b*, Malpighian layer, with islets of connective tissue; *c*, connective tissue; *d*, section through columns of cells of Malpighian layer appearing as cell-nests; *e*, transverse and oblique sections of projecting columns of epithelium, in some of which (*f*) the central cells have become horny. × 40.

packed as ultimately to become hard and dry like those of the nails and hair; the globes are then of a brownish-yellow color and of a firm consistence. These globes are often large enough to be readily

visible to the naked eye, and, owing to the onion-like arrangement of the epidermic scales, they usually present a fibrous appearance.

The **stroma** presents every variation between rapidly growing embryonic and incompletely fibrillated tissue. It may be tolerably abundant or almost entirely wanting. It rarely forms such a marked alveolar structure as that which characterizes the other varieties of carcinoma, and consists simply of the fibrous tissue of the part more or less infiltrated with small round cells, which may be ultimately replaced by connective tissue.

The development of squamous epithelioma is due to the down-growth of the surface-epithelium of skin or of certain mucous membranes into the connective tissue and deeper parts, as is described on page 137. The tendency of epithelioma is to break down and ulcerate at an early stage: the breaking down is due to fatty degeneration of the cells, and not to inflammation.

To the **naked eye** epithelioma usually presents itself as a small hard ulcer; as an indurated fissure; or as a subcutaneous nodule, which subsequently breaks down. The surface of the ulcer is irregular, and may be sloughy. It is often clean, and covered by large firm, bluish-red granulations, consisting largely of epithelium; more rarely the surface is markedly warty. The tumor itself is firm in consistence, often more or less friable, and, on section, presents a grayish-white granular surface, sometimes intersected with lines of fibrous tissue. The cut surface yields on pressure a small quantity of turbid liquid. In many cases a peculiar, thick, crumbling, curdy material can also be expressed, which often comes out in a worm-like shape, suggestive of sebaceoüs matter from the glands of the skin. This material is very characteristic. It is composed of fatty epithelial scales, and on being mixed with water it does not diffuse like the juice of other cancers, but separates into minute visible particles. If it is very abundant, the cancer is soft and friable, and the material can be seen on the cut surface as small scattered opaque dots.

Irritation is believed to have more to do with the causation of squamous epithelioma than of other kinds of cancer. Some, such as cancer of the scrotum from soot, and epithelioma of the arm in workers with tar or paraffin, appear to be due simply to irritation in people the physiological resistance of whose connective tissue is diminished until invasion by epithelium is rendered easy. Other epitheliomata occur at points where, the process of development being complicated, errors are likely to have occurred. These places have been already enumerated (p. 95). Many of these are points exposed to irritation. Squamous epithelioma usually infects the neighboring lymphatic glands, but rarely forms metastatic growth in internal organs.

Rodent Ulcer.

Rodent ulcer is a form of squamous epithelioma beginning as a pimple upon the nose or cheek, and liable to frequent irritation from

FIG. 82.

Rodent ulcer of nose. The patient had small rodent ulcers of the nose and cheek, and an early epithelioma of the lip. × 50. (Boyd.)

rubbing or picking. After a time it breaks down, and the ulcer thus formed slowly spreads, destroying everything that it meets, including bones, and producing the most hideous deformity. This may go on for many years, the health remaining good and no gland being affected. Rodent ulcer is the least malignant form of cancer. It occasionally shows a tendency to cicatrize, and at places may even become covered with normal epithelium. It differs from ordinary squamous epithelioma chiefly in the small size of the cells, in the absence of prickle-cells, in the slight tendency the cells show to become scaly and to form nests, and in the ease with which the epithelial columns can be traced (Fig. 82). Some authorities believe that rodent ulcer begins in the root-sheaths of the hairs or in the gland-epithelium of the skin. In some cases having the characteristic history of rodent ulcer, the structure is that of typical squamous epithelioma.

III. Columnar Epithelioma.

The terms *columnar epithelioma* and *adenoid cancer* are applied to those forms of epithelial cancer which grow from mucous membranes with columnar (cylindrical) epithelium—*e. g.*, the stomach and intestines, and especially the rectum and uterus. In these tumors the epithelial elements are similar to those of the mucous membrane from which they grow. They are cylindrical in shape, and are arranged perpendicularly to the walls of the alveoli in a manner precisely analogous to that of the columnar epithelium on the mucous surface (Fig. 83). The slower the growth, the more typical the gland-formation. In rapid growths, and in recurrences, the cells are small and the lumina imperfect. The latter may be filled up, and the growth be indistin-

guishable from acinous cancer, except by its edge, where a low columnar or cubical form usually persists; but this too may be lost. The growths are of a soft and often gelatinous consistence; they show a marked tendency to undergo colloid degeneration. These tumors cause secondary growths in the lymphatic glands, and sometimes in the liver, lungs, and bones: the secondary tumors possess the same characters as the primary cancers. Columnar epitheliomata are generally less malignant than the acinous forms.

At an early stage the growth penetrates the muscularis mucosæ and invades the deeper structures, thus differing from an adenoma. It ulcerates with extreme readiness.

Fig. 83.

Columnar epithelioma. From the colon. × 100.

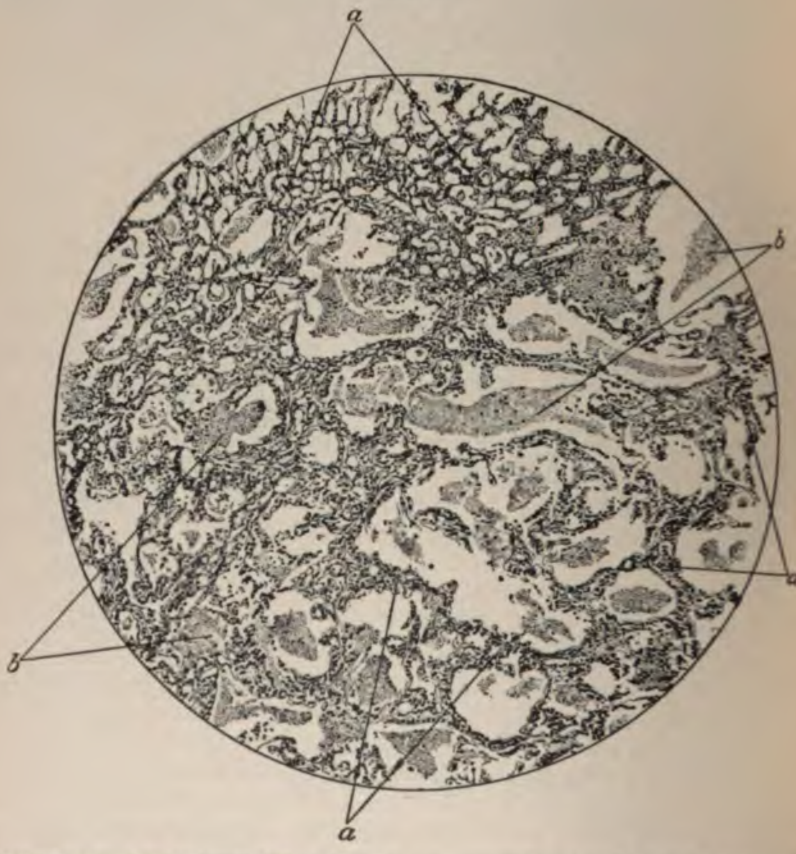
Colloid Cancer.

Colloid cancer is simply one of the preceding forms which has undergone mucoid or colloid degeneration. Sarcomatous and other non-cancerous growths may undergo the same change.

The alveolar structure in colloid cancers is very marked. The alveoli have very thin walls; they are large, distinct, and more or less spherical in shape. The large size and distinctness of the alveoli is owing to their distention by products of degeneration. These products form a gelatinous colloid material, which is glistening, translucent, colorless, or yellowish, and of the consistence of thin mucilage or size. In the main it is perfectly structureless (Fig. 84); within the masses of colloid material, however, are imbedded varied numbers of epithelial cells. These cells present a peculiar appearance: they are large and spherical in shape, and are distended with drops of the same gelatinous material as that in which they are imbedded. In some cases they may display a lamellar surface, their boundary being marked by concentric lines (Fig.

24). It would appear that the colloid change commences in the cells, which are gradually destroyed in the process. In other cases, indistinguishable by the naked eye, the cells, with the exception of slight *fatty degeneration*, are but little affected, and the substance distending the alveoli is more viscid and mucoid in character. This is due to a *mucoid degeneration* of the intercellular substance rather than to a colloid change commencing in the cells.

FIG. 84.



Colloid cancer, from the wall of the stomach. *a,a*, cancer-cells arranged in alveoli; *b, b*, masses of colloid material.

Colloid degeneration is most frequently met with in cancers of the abdomen, especially those of the stomach, intestine, ovary, and peritoneum. The tendency of abdominal tumors to undergo colloid degeneration is, at present, unexplained.

CHORIO-EPITHELIOMA.

The name chorio-epithelioma, or deciduoma malignum, has been applied to a peculiar form of growth occurring in the uterus after pregnancy, and associated with hydatidiform degeneration of the placenta. Histologically these tumors consist of cells resembling those forming the covering of the chorionic villi (Langhans' layer), but grouped in columns, several cells thick, instead of in a single layer;

FIG. 85.

Chorio-epithelioma of uterus. *a*, interior of villus; *b*, large epithelial cells; *c*, syncytium, or undifferentiated protoplasm containing nuclei.

along with these are found masses of protoplasm containing many nuclei, but not differentiated into cells (*Syncytium*). The whole structure thus closely resembles that of the chorionic villi, from which the growth is supposed to arise. The great pathological interest of this form of tumor is due to the apparent possibility of one individual—the mother—being "infected" with cells from another individual—the fœtus—these cells then proceeding to form a malignant tumor. The facts, if rightly observed, appear to support the theory of tumor-

formation set forth at the beginning of this section (p. 88). Metastatic growths occur in the lungs and other parts. Hemorrhage often takes place into these tumors, so that their structure is obscured. Tumors similar in structure have been met with in the testis and the mediastinum; in these positions they are to be regarded as teratomata, analogous to dermoid cysts.

TERATOMATA.[1]

These are congenital tumors occurring chiefly as projections from the sacral region (*coccygeal tumors*), or from the head or neck—points at which double monsters are often united. Sometimes teratomata are placed within the abdomen or other part of the body and cause no actual projection. Some of them are due to the inclusion and imperfect development of one embryo within another; others to the excessive and disorderly development of a portion of the tissues of a single fœtus. Teratomata are most complex, and may contain all the tissues of the body up to ganglion-cells, more or less confusedly mixed. They may be very large at birth, or may not attract notice till later.

Dermoid cysts belong to the same group. Their walls (Fig. 86) are

FIG. 86.

Dermoid cyst of the ovary. Showing all the structures of true skin except sweat-glands—viz., epithelium, rudimentary papillæ, fibrous tissue or cutis vera, hair follicles, and large sebaceous glands. × 18. (Boyd.)

composed of skin and of any of the structures ordinarily arising from skin. All varieties of connective tissue may also be found in the walls. The cysts contain epithelial products, coils of long hair, teeth, and even bones. They may occur anywhere, but are commonest in the ovaries, testicles, and subcutaneous connective tissue. In many cases they seem to be due to the inclusion of a piece of epiblast, and are analogous to

[1] Greek τέρας, a marvel. [2] Greek δέρμα, skin.

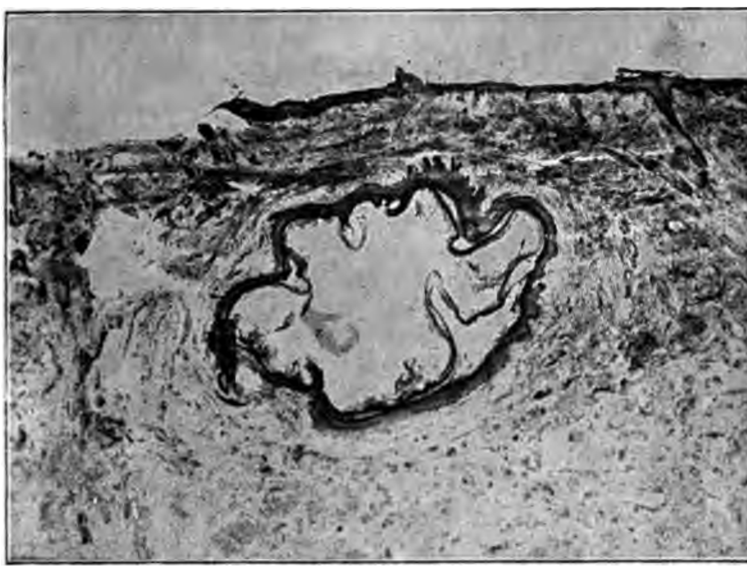
the implantation-cysts which are occasionally produced by the inclusion or "healing in" of a piece of skin during life (Fig. 87).

CYSTS.

In addition to the new-growths already described, there is a large class of formations, many of which cannot be regarded as "tumors," in the strict application of this term. These are the *cysts* or *cystic tumors.*

A **cyst** is a cavity containing liquid, gelatinous, or pultaceous material, which is separated from the surrounding structures by a more or less distinct capsule. It may be (1) part of a new-growth; or (2) a pre-existing structure which has become distended by its own secretion,

FIG. 87.



Implantation-cyst, in abdominal wall, removed on the supposition that it was a recurrent nodule of a growth removed by laparotomy about a year before. It was probably due to the growth of a fragment of skin which had been inverted at the time of the operation and severed from its original connections. (From a specimen by Dr. Rolleston.) × 9.

by a growth from its lining wall, by the extravasation of blood or other fluid into it, or by some more complex process. Only a minority of these come within the category of new-growths; but, for the sake of convenience, they will all be considered together.

The accumulation of secretions and of other products within pre-existing cavities may be effected in the three following ways:

(1) By the retention of the normal secretion owing to the closure of the excretory ducts, as so often occurs in sebaceous glands (*retention-cyst*).

(2) By excessive secretion, the cavity being unprovided with an excretory duct, as in the distention of bursæ.

(3) By the extravasation of blood into the cavity, as in the sac of the tunica vaginalis (*hæmatocele*).

The independent formation of a cyst may take place—

(1) By the softening and liquefaction of the tissues in some particular part, owing to mucoid or fatty changes, or to colliquative necrosis. The tissues around the softened matters become condensed, and ultimately form a kind of cyst-wall, as in the small subchondral cavities sometimes seen in rheumatoid arthritis.

(2) By the collection of fluid in certain connective-tissue spaces, and the subsequent enlargement and fusion of these spaces. The surrounding tissue becomes condensed, and forms a cyst-wall; and this may in some cases become lined with flattened connective-tissue cells (endothelium). In this way a *false bursa* is formed.

(3) By the formation of a cyst-wall round foreign bodies, parasites, or extravasated blood; the wall consists of fibrous tissue, and is the result of the reaction of the surrounding tissues to the irritation produced by the foreign substance. Smooth, heavy, sharp-edged foreign bodies are particularly liable, during the process of "healing in," to produce cysts of this character, especially when the parts are not kept at rest. Salzer has suggested the artificial introduction of such substances when adhesions are feared or a false joint desired.

Structure.—The **wall** of the cyst will vary in its nature according as it is that of a pre-existing or a newly formed cavity. In the former case, it will possess a lining which will present the same characters as that of the gland, serous membrane, or other structure from which the cyst originated. If the cyst is of independent formation, there is at first no endothelial lining to the fibrous capsule, but one may develop later, as in false bursæ. The cyst-wall is sometimes firmly connected with the adjacent parts, so that it can only with difficulty be separated; in other cases the union is much less intimate. Instead of being a distinct structure, it may simply consist of the surrounding tissue which has become dense and fibrous in character.

The **contents** of cysts are very varied, and may serve as a basis for their classification. In the retention-cysts they will vary with the nature of the normal secretion. Serum, sebaceous matter, saliva, milk, seminal fluid, and other substances are found in these cysts: they are more or less altered in character from having been retained in a closed cavity. In the exudation-cysts serum is the most frequent constituent; and in extravasation-cysts, blood. In those cysts which originate from the softening and breaking down of tissue the contents are formed from the products of degeneration, such as mucin, fatty matters, and serum.

Cysts may be **simple** or **compound**. A simple cyst consists of a single cavity (*loculus*). A compound or multilocular cyst is one consisting of numerous loculi, which either communicate with one another or remain isolated. Another variety of compound cyst is one with

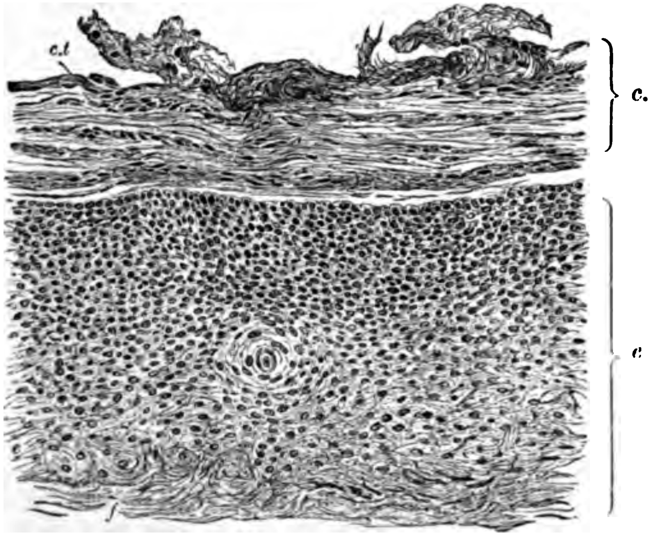
[1] Greek αἷμα, blood; κήλη, a swelling.

endogenous growths, or, in other words, a large cyst with others growing in its walls. A compound cyst may become a simple one by destruction of the walls separating individual loculi.

Cysts are frequently associated with other growths, hence the terms, "cystic sarcoma," "cystic cancer," etc. It is especially in those growths which originate in glandular structures, as in the mamma, testicle, and ovary, that this combination is met with. The cystic development may almost entirely obliterate the structure of the tumor in which it takes place, so that ultimately the latter may become converted into a mere congeries of cysts, as in *compound ovarian cysts* and *cystic kidneys*. In other cases large papillary masses of the tumor grow into the cystic cavities (*compound proliferous cysts*). Considerable difficulty in determining the nature of the original growth is thus not infrequently experienced.

Secondary Changes.—These may take place in the wall of the cyst or in its contents. The *cyst-wall* itself may become the seat of new-growths, and produce secondary cysts, villous, glandular and other structures: this process occurs in many compound ovarian cysts (p. 135).

FIG. 88.



Sebaceous cyst. *c. t*, the thin connective-tissue layer forming the outside of the wall, lined by a thick layer of epithelium (*e*). The outer cells of the latter layer are somewhat cubical; while the inner are flattened, and are succeeded by fatty débris, which forms the innermost part of the wall, and is (*f*) so compressed as to have a fibrous aspect. (Boyd.)

It may also be the seat of an inflammatory process, which terminates in suppuration and granulation; by this means the cyst frequently becomes obliterated, its contents being either absorbed or discharged externally, and the cavity closing by granulation. Calcification and ossification of the wall may also occur. The *contents* may become altered in character, thickened, and viscid. Epithelial elements undergo fatty

changes, and so give rise to cholesterin-crystals. Calcification of the contents is also common.

Varieties.—Cysts may be most conveniently classified according to their mode of origin, thus:

I. *Cysts formed by the accumulation of substances within the cavities of pre-existing structures.*

(1) **Retention-cysts.**—Cysts resulting from the retention of normal secretions. These include:

a. *Sebaceous Cysts.*—These are formed by the retention of sebum in the sebaceous glands. The cysts possess a very thin connective-tissue wall lined by stratified epithelium (Fig. 88). They contain a mass of fatty epithelium and its products, cholesterin and amorphous débris. Many sebaceous cysts are really neoplasms, and are classed as *cystic adenomata.*

b. *Mucous Cysts.*—These are formed by the retention of secretions in the glands of mucous membranes.

c. *Cysts from the retention of secretions in other parts,* including *ranula,* from occlusion of the salivary ducts; *encysted hydrocele* from occlusion of the tubuli testis; *mammary cysts,* from obstruction of the lacteal ducts; *simple and some compound cysts of the ovary,* from dilatation of the Graafian follicles; and simple *cysts of the kidneys* from local obstruction.

(2) **Exudation-cysts.**—Cysts resulting from excessive secretion in cavities unprovided with an excretory duct. These include *bursæ, ganglia, hydroceles, meningoceles, cystic bronchoceles,* and many *cysts in the broad ligament.*

(3) **Extravasation-cysts.**—Cysts resulting from extravasation into closed cavities. These include *hæmatocele,* and some other forms of sanguineous cysts.

II. *Cysts of independent origin.*

(1) **Cysts from Softening of Tissues.**—These are especially common in new formations, as in chondroma, lipoma, sarcoma, etc.

(2) **Cysts from Extravasation into Solid Tissues**—*e. g.,* into brain, or soft new-growths.

(3) **Cysts from Expansion and Fusion of Spaces in Connective Tissue**—*e. g., false bursæ,* originating from irritation and exudation into the tissues.

(4) **Cysts formed around Foreign Bodies, Extravasated Blood, and Parasites.**

(5) **Congenital Cysts.**—Many persistent fœtal structures (p. 25). *Dermoid cysts.*

(6) **Cysts forming part of the growth of Parasites**—"cystic stage" —(*cysticercus cellulosæ, hydatids*). See "Animal Parasites."

CHAPTER VI.

IRRITATION AND REPAIR.

INFLAMMATION.

INFLAMMATION is a clinical term of great age, and suffers from the same disadvantage as other clinical terms adopted by pathologists, inasmuch as each successive discovery concerning its nature necessitates a wider divergence between its clinical and pathological connotations. For centuries, inflammation was known as the condition characterized by the presence of *redness, swelling, heat,* and *pain*—the cardinal signs of inflammation. Later on, two others were added—*tenderness* and *impaired function.* It was next gradually recognized that inflammation is a process rather than a condition; and it was accordingly defined as the "succession of changes which takes place in a living tissue as the result of some kind of injury, provided that this injury be insufficient immediately to destroy its vitality" (Sanderson).

Modern experiments have led pathologists to consider that the processes comprised in inflammation represent, and can best be described as, *the reaction of the tissues to irritation.* The reaction of the tissues under such circumstances is very complex and varies both with the irritant and with the tissue. It has, therefore, become increasingly difficult to connect and classify all the possible manifestations of this reaction. To avoid these difficulties some pathologists have advocated the abolition of the term "inflammation," on the ground that it deceives by suggesting the presence of a single process which in reality has no clearly defined existence. The term has, unfortunately, obtained too firm a hold on pathological conceptions to permit of its being readily discarded.

In this chapter we shall first take four selected instances of tissue-irritation and describe the phenomena they exhibit; then proceed to discuss and, as far as possible, to explain these various phenomena; and finally conclude with a description of the varieties and causation of the different processes which are at present regarded as inflammatory, including the repair of the damaged tissues.

Reaction of Tissues to Injury.—1. Simple Repair.—To a minute spot in the centre of the anterior surface of the cornea Senftleben applied a solution of chloride of zinc, which soaked through the dense anterior corneal lamina without destroying it. By this method he found it was possible to kill the corpuscles immediately underneath the affected area of the cornea without influencing the marginal vessels. The cornea remained quite clear, showing no naked-eye change; but, on the third day, microscopic examination showed that the swollen

corneal corpuscles round the damaged area were shooting processes into it. By normal karyokinesis, these cells gradually replaced those destroyed until the corneal corpuscles were completely restored. In this instance of tissue-reaction we have simple destruction on the one hand and simple regeneration on the other. Instances of a process as simple as this are difficult to obtain.

2. Simple Inflammation.—If the web of a frog's foot, or some other piece of thin transparent tissue, be placed under a microscope, and the

FIG. 89.

Small vein in mesentery of dog, after exposure for half an hour and irrigation with salt solution. *a*, red corpuscles; *b*, leucocytes adhering to wall of vein; *c*, red corpuscles; *d*, leucocytes which have escaped from vessel; *e*, leucocyte in act of escaping; *f*, fibrous tissue. × 340. (Modified from Thoma.)

part under observation be touched with a drop of chloroform or other volatile irritant, a definite series of changes can be observed. The first of these is a distinct *dilatation* of the arterioles, then of the veins, and about an hour afterwards, of the capillaries. The dilatation progresses steadily and is accompanied by some increase in the length of the vessels, so that they become slightly tortuous. The arterioles are affected most, then the veins, and, least of all, the capillaries. This enlargement of the bloodvessels is at the onset accompanied by a temporary *acceleration* in the flow of the blood. If the injury has been extremely slight, the vessels and circulation may at this point gradually return to the normal; but, in the large majority of cases, by the time the dilatation is complete, this acceleration begins to give place to progressive *retardation*, the vessels still remaining dilated. Pulsation can now be observed in the smallest arteries; and the blood-stream is slow enough for the observer to distinguish the individual corpuscles in the capillaries and smaller veins, and sometimes even in the arterioles. The

retardation of the blood-current may take place rapidly, and is always first observable in the veins.

As the blood-current becomes slower, the axial stream becomes broader; and white corpuscles, in increasing numbers, fall into the marginal stream—rolling slowly along, stopping here and there, and finally coming to a standstill (Fig. 89). Thus the smaller veins become lined with leucocytes. Somewhat similar, but less complete, changes occur in the capillaries. In the meantime the distinction between axial and marginal streams completely disappears, and the vessels

Fig. 90.

Subcutaneous tissue some distance above dead part in a case of spreading gangrene. Three veins packed with leucocytes (*l*), which are escaping freely. Round the artery (below) there are none. Outside the vessels many larger cells are seen. × 200.

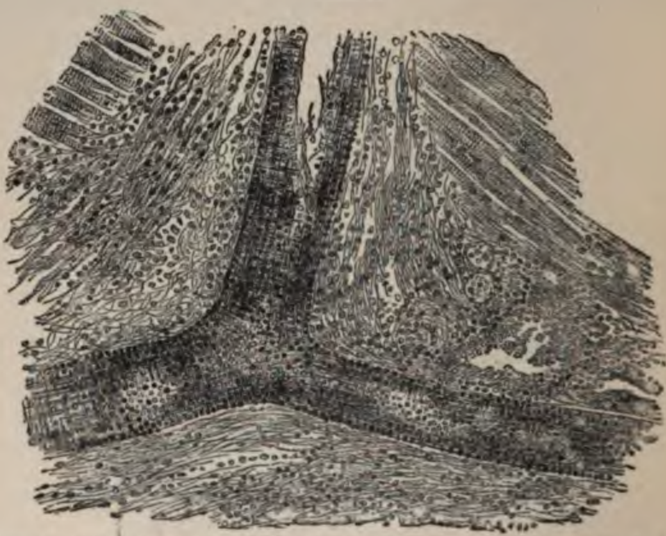
become filled with both red and white corpuscles (Fig. 90). Actual measurement shows that the vessels may be at least one-fourth larger than natural. After a time all onward movement ceases in the capillaries, and their contents sway to and fro with the pulse. This is known as the stage of *oscillation*, and is succeeded by that of *stasis*, in which no movement of any kind occurs. In the severest cases, thrombosis may take place; this always occurs when the capillary walls are dead (p. 32).

If a small vein lined by leucocytes be carefully watched, some of the leucocytes immediately adjacent to the wall can be seen gradually sinking into it and passing through into the surrounding tissues. The actual passage of the leucocytes through the wall cannot ordinarily be observed. Small button-shaped elevations appear on the outer side of the wall of the vessel. These gradually enlarge, assuming the form of irregular, pear-shaped bodies adherent by their small ends to the vessel-wall, and often send out processes whilst so attached (Fig. 89).

Ultimately, the small pedicles of protoplasm give way, and the corpuscles are free outside the vessel. A similar escape takes place, but to a less extent, from the capillaries (*diapedesis*).

As a rule, in inflammation the escape of white corpuscles greatly exceeds that of the red (Fig. 91); but in some cases, in which almost complete stagnation is induced in a large number of capillaries, the

FIG. 91.



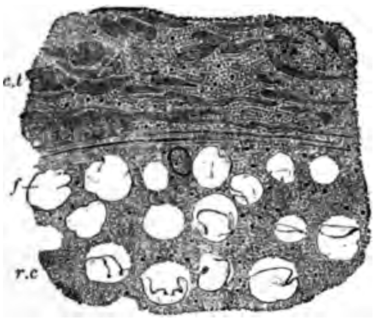
Acute rheumatic myocarditis. The tissues around the artery, seen in longitudinal section, are infiltrated with leucocytes; hemorrhage (*h*) has occurred from the longer branch. × 20. (Mott.)

usual state of affairs may be reversed (Fig. 92). From such capillaries the red corpuscles pass out in great numbers—probably between the endothelial cells—occupy the interstices of the tissues, and give the exudation a hemorrhagic character. Several may escape in quick succession from one place, giving rise to a red spot, visible to the naked eye as a punctiform hemorrhage (Fig. 97). No gross rupture of the vessel-wall occurs, as may be shown by injecting the vessels. On the other hand, when *retardation has not culminated in stasis*, most red corpuscles remain within the vessels and pass along through the inflamed area, whilst the leucocytes, adhering to the walls, become elongated and pear-shaped from the influence of the passing blood-stream, as just described.

Both red and white corpuscles at first remain near the vessels whence they have escaped; but they are soon pushed away by other corpuscles, or washed on by the escaping fluid. The white corpuscles have, in addition, their own peculiar power of locomotion, stimulated and directed by the chemical products in the neighborhood of the irritation (*chemotaxis*, p. 179); for this reason they may ultimately be

found far from their place of egress. When absolute stasis occurs the emigration of corpuscles ceases.

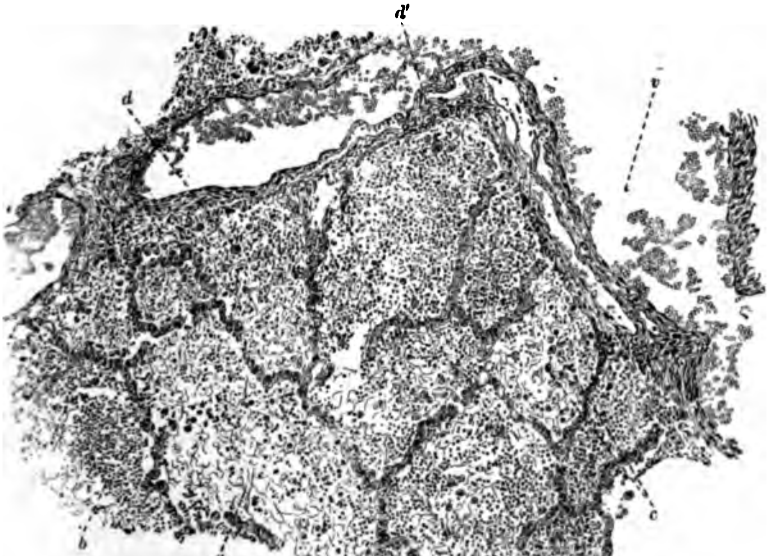
FIG. 92.



Deeper layer of cutis and subcutaneous fat, a short distance above the dead part in a case of spreading gangrene. The interstices of the tissues are crammed with red corpuscles, among which are a few leucocytes. *c.t*, connective tissue; *f*, fat-cells; *r.c*, red corpuscles. × 150. (Boyd.)

While these visible changes are in progress, a much larger amount of fluid than naturally escapes from the vessels passes into the sur-

FIG. 93.



Coagulated inflammatory exudation into alveoli of lung in a case of acute pneumonia. *a*, alveolus containing fibrin-filaments and a few blood-corpuscles; *b*, alveolus containing a larger proportion of corpuscles; *c* and *d*, desquamated alveolar epithelium; *v*, vein. × 120.

rounding tissues. Moreover, the exuded fluid differs in composition from the normal lymph. The greater the damage to the vessels the

more nearly the exudation approximates to the liquor sanguinis, and the greater the number of corpuscles it contains (Fig. 93).

By the time all these events have occurred, the irritant may have disappeared, and the consequent vascular changes just described have begun to subside. If the extreme periphery of the inflamed area be closely watched, the corpuscles of the stagnant blood will be seen to move off one after another, until a slow stream is re-established through the inflamed area. This stream quickens as resistance diminishes, and contraction of the vessels follows the gradual recovery of power by their muscular coats. Exudation, first of corpuscles, then of fluid, ceases, and the circulation again becomes normal.

The cells are removed mainly by the lymphatics; the exuded fluid also escapes by the lymphatics and, after restoration of the circulation, by the veins as well. In the later stages any unremoved blood-corpuscles or fibrin undergo fatty degeneration, and thus the complete removal of the inflammatory products is much facilitated. Any endothelial or connective-tissue cells, which may have been destroyed by the irritant, are replaced by multiplication of the surviving cells, and the recovery of the inflamed tissue is complete.

The changes which occur in the *healing of wounds* furnish good illustrations of the phenomena of inflammation just described.

(1) **Healing by First Intention.**—If an incision through the skin and underlying structures be made by a sharp and perfectly clean instrument, and no subsequent infection of the wound be permitted, the following changes can be observed. The incision through the capillaries, arterioles and venules will be followed by a small amount of hemorrhage, and the damaged vessels will dilate. If no large bloodvessel has been injured, the hemorrhage will quickly cease, as the divided vessels become plugged by thrombi—the thrombosis extending in each vessel to the nearest collateral branch. If the cut surfaces remain apart, and such blood as may have collected on them be removed, they will gradually acquire a shiny or glazed appearance. This glaze is formed by exudation of fluid and cells from the neighboring vessels, in the manner just described as occurring in the web of the frog's foot. At first there will be a large proportion of red corpuscles in the exudation, but this proportion will rapidly diminish and the coagulating fluid will then become clear and yellow. If the cut surfaces be now brought into exact apposition throughout their whole extent, they will become glued together by the exudation, some of which will infiltrate the tissues in the immediate neighborhood and some escape between the edges of the wound, thus reaching the surface of the skin. If the wound is large and deep, and the exudation considerable, it is necessary to provide channels to facilitate the escape of the exudation. The same events will occur if the cut surfaces be brought together directly the bleeding has ceased.

Microscopic examination, on the second day after the injury, shows the cut surfaces of the wound connected by a narrow layer of coagulated exudation and leucocytes; while the tissues in the immediate neighborhood of the incision are swollen and granular and much infiltrated with

leucocytes. These are apparently instrumental in removing such minute portions of the original tissue as may have been killed by the injury. As the leucocytes disappear they are gradually succeeded by cells derived from the neighboring uninjured connective tissue; while, on the external surface of the wound, the epithelium multiplies and covers the edges of the wound. In the meantime connections are also established between the cut vessels in a manner that will subsequently be described (p. 189). All these changes may be complete in a few days—less than a week—though they often take longer (Fig. 93); but if the cells of any more

FIG. 94.

Healing of an incised wound of the skin united by suture—sixth day. *a*, epidermis; *b*, corium; *c*, fibrinous; *c'*, hemorrhagic exudate; *d*, newly formed epithelium, containing numerous karyokinetic figures, and showing epithelial plug projecting into exudate lying beneath; *e*, karyokinetic figures at some distance from line of incision; *f*, new connective tissue growing from connective-tissue spaces and containing cells with karyokinetic figures and bloodvessels with growing walls; *g*, developing connective tissue with leucocytes; *h*, collection of leucocytes at the lower angle of the wound; *i*, fibroblasts lying inside the exudate; *k*, sebaceous gland; *l*, sweat-gland. × 75. (Ziegler.)

specialized tissues have been destroyed, their regeneration, if it occur at all, will not begin until the repair of the connective tissue is complete (Fig. 94).

This form of healing will not occur if the surfaces of the wound are left gaping superficially, or are separated in their deeper parts by foreign bodies, blood, or any considerable quantity of exudation; nor will it occur

if the surfaces are allowed to move one on the other; nor if any considerable portion of the tissues has been destroyed; nor if pyogenic organisms or any other source of irritation are admitted.

It often happens that in an extensive wound, however accurately adjusted, small collections of blood-clot will be found here and there in

FIG. 95.

Laparotomy wound—sixteenth day. *a*, epithelium: *b*, corium; *c*, subcutaneous fat; *d*, vessels in scar-tissue of corium; *e*, newly-formed epithelial layer; *f*, vessels in subcutaneous scar-tissue. × 40. (Modified from Ziegler.)

the course of the incision, wherever hemorrhage from an imperfectly plugged vessel has caused separation of the surfaces. At such places the healing process is somewhat different. The vascular changes already described will occur and the clot will thus become surrounded by the exuded fluid and leucocytes; the latter will gradually penetrate the clot and destroy the red corpuscles. The leucocytes will be followed by cells derived from the fixed cells and plasma-cells of the surrounding connective tissue; and the organization of the mass will gradually follow (p. 173).

(2) **Healing by Granulation.**—If the cut surfaces of the original wound are permitted to remain apart, so as to form a large and open cleft, the healing process is much slower. The *glaze* on the surface of the wound liquefies and disappears; a larger amount of the damaged tissue dies; a greater number of leucocytes make their way from the vessels to the surface; and the vascular phenomena extend over a somewhat larger area.

The uninjured connective-tissue cells situated immediately below the wound gradually multiply, and at the same time new capillaries develop from the endothelium of the nearest surviving vessels (p. 181), and form loops which penetrate into the layer of leucocytes now closely

FIG. 96.

A granulating surface. *a*, layer of pus-cells; *b*, granulation-tissue with loops of bloodvessels; *c*, commencing development of the granulation-tissue into a fibrillated structure. (Rindfleisch.) Diagrammatic.

aggregated in the most superficial stratum of the wound (Fig. 97). On section, a few days after the injury, there may be seen, immediately above the undamaged tissue at the base of the wound, numbers of fibroblasts in various stages supplied with developing vessels, and, superficial to this, leucocytes and fibroblasts arranged round the summit of the capillary loops so as to form a number of small red points or granulations, from which this method of healing takes its name. Thus the wound is gradually and permanently filled up by the multiplication of the surviving connective-tissue elements—plasma-cells and fixed cells. As the granulation-tissue reaches the level of the skin, the epithelium at the surrounding edge multiplies and, gradually extending, covers the intervening space. Many of the new bloodvessels subsequently become obliterated, and the new tissue, known as *scar-tissue* (p. 174), though for a time pinker in appearance than the surrounding parts, becomes later on whiter and denser than the tissue around it. Healing by granulation is necessarily a much slower process than heal-

ing by first intention; while infection by micro-organisms is m
likely to occur. The presence of organisms on the surface of a gra
lating wound will lead to the death of many of the leucocytes and
most cases, to the formation of pus (p. 173).

FIG. 97.

Granulation-tissue from an open wound with fibro-purulent deposit. *a*, granulation-t
b, fibro-purulent deposit; *c*, bloodvessels. × 150. (Ziegler.)

(3) **Union of Two Granulating Surfaces.**—When two surfaces h
granulated as above described, they may sometimes be caused to u
if brought together, thus saving much of the time which woul
required for filling up from below. The presence of micro-organ
and imperfect drainage will prevent such union. This is the wa
which abscesses should heal when their walls are allowed to fall
gether by evacuation of the pus (p. 171).

(4) **Healing Under a Scab.**—This form of healing is possible w
the wound is small and the exudation forms a scab as it dries on
surface. It is not common in man, except in superficial abrasi
The formation of granulation- and scar-tissue takes place beneath
scab, as also does the inward growth of epithelium. When the sur

th the scab is completely covered with epithelium, the scab drops The dry scab is but slightly irritant in itself, and does not putrefy. tempt is made to imitate this process, when wounds, such as those ig to cavities, are closed with collodion; or when blood or tincture

FIG. 98.

abscess in a case of septic embolism of the kidney. *a*, leucocytes advancing toward and rounding *b*, a mass of cocci, in whose neighborhood all trace of structure has disappeared; *c*, renal epithelium too damaged by bacterial products to take the stain; *d*, kidney- ie staining normally; *e*, vein from which leucocytes are making their way to the comicing abscess. × 100.

izoin on lint is allowed to dry and occlude the opening. Such ient is, however, dangerous; for if septic or infective organisms

have entered the wound, they will probably excite inflammation, and the absence of drainage will be most prejudicial.

(5) **Suppurative Inflammation.**—If a portion of a culture of the *Staphylococcus pyogenes aureus* be injected into the subcutaneous tissue of a rabbit, the organisms thus deposited will, under ordinary circumstances, multiply and produce an abscess.

In the course of a few hours vascular changes, precisely similar to those described in the preceding section, can be observed in full progress. Considerable numbers of leucocytes of the large uninucleated and, later on, of the multinucleated variety (p. 178), make their appearance in the affected area. Cocci may be found not only at the point of inoculation, but at some little distance from it. Some will be lying free in the tissue, but most will have been taken up by the cells of the part—whether leucocytes, fixed connective-tissue corpuscles, or endothelial cells of the capillaries.

During the next twenty-four hours the cocci, on the one hand, multiply rapidly and pass into the adjoining lymph-spaces, while the multinucleated leucocytes, on the other hand, collect in increasing numbers until they have completely surrounded the cocci (Fig. 98).

By the end of the second day there are generally several central

FIG. 99.

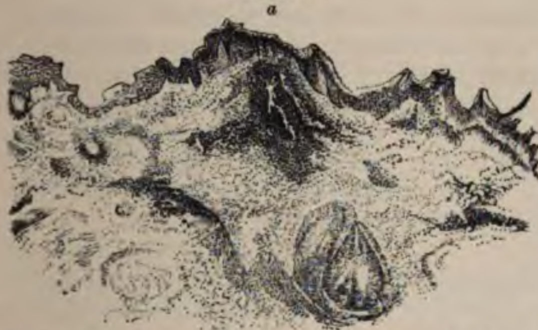
Section through a smallpox pustule. The horny layer over the centre of the surface has disappeared, and the free edges are shown. A mass of cells is seen in the boundary between the swollen Malpighian layer and the true skin, making its way to the surface. Thus the actual lesion is situated wholly in the epidermis, while the fluid and cells have passed up from the derma, the track being shown. (Compare Fig. 100.) (Boyd.)

masses of cocci imbedded in, and surrounded by, a well-defined zone of leucocytes. The portions of the original tissue in which the masses of cocci lie do not stain, for, owing to the proteolytic action of the products of the cocci, all vessels and other evidences of structure have disappeared, except the multinucleated leucocytes with which the area has become more or less crowded. Many of the leucocytes show degenerative changes (fragmentation of nuclei), but in none of them, or of the tissue-cells in their neighborhood, are any evidences of repair (*karyokinesis*) to be made out at this stage. In the outer part of this zone the tissue is also crowded with leucocytes, the large uninucleated variety being now confined to the periphery. In the extreme periphery, persistent remnants of the original tissue-cells may be seen. Beyond

the actual limits of this mass of cocci and leucocytes (*abscess*) the vessels are dilated and present the vascular changes previously described; while here and there cocci may be found in the lymph-spaces, in the endothelial cells of the capillaries, or in the interior of the leucocytes.

If the affected area be examined a few days later, further changes will be seen to have taken place. The centre of the abscess consists of cocci, leucocytes, and fatty débris in an albuminous fluid (*pus*). Around the pus, which is immediately encircled by a zone of living leucocytes, a barricade of new cells consisting mainly of *fibroblasts* (p. 173) has appeared, and in it a series of new capillary loops in connection with the neighboring and pre-existing vessels. This constitutes the so-called *granulation-tissue* (p. 168), and forms a wall in which there are no cocci and but few leucocytes.

FIG. 100.



An abscess in the skin. The horny layer has largely disappeared, and the Malpighian layer is pushed upward by the subjacent abscess (*a*). The mass of pus-corpuscles is just breaking down to form a cavity, the walls of which are thickly infiltrated with similar cells. (Compare Fig. 99.) (Boyd.)

If the pus and the surviving cocci be completely removed, and the entrance and growth of other organisms prevented by antiseptic precautions and efficient drainage, the cavity will disappear by the gradual extension of the granulation-tissue toward the opening until the walls meet, assisted, in some cases, by the collapse of its sides. The permanent obliteration of the abscess-cavity is ensured by the union of the walls and by the development of the constituent fibroblasts into cicatricial fibrous tissue.

If left unopened, an abscess generally extends or shifts its position. The direction of its advance is due to the growth of the cocci and the action of their products: the extension is marked by thrombosis in the dilated vessels and necrosis of the cells they supply, as well as by emigration of leucocytes and exudation of fluid into the newly affected area just beyond, followed by a progressive repetition of the changes just described. The former site and track of the abscess is marked by the formation of granulation-tissue and, later on, of cicatricial fibrous tissue. The progress of an abscess is rarely arrested until

it reaches some free surface or open cavity, upon or into which it bursts. On section of the wall of a spreading abscess, all the stages of inflammation can be seen. In the centre, necrosis; in the vessels, as we pass outward from the centre, thrombosis, stasis, retardation of flow—diminishing, and perhaps giving place to acceleration, before the normal circulation is reached: in the tissues the usual exudation and diapedesis are found accompanying the retardation of the blood-flow. This account explains how it is that the presence of redness, heat, and œdema over a deep-seated swelling leads us to infer the occurrence of suppuration as the cause of the swelling.

Diffuse suppuration is a similar process going on over a wide area. The damage to the tissues is often more intense than when the phenomena are circumscribed, and it is by no means uncommon to find shreddy sloughs in the pus, for the effect of the injury on some portions of tissue is so great as to cause death of large masses of cells simultaneously. Diffuse suppuration is generally due to the *Streptococcus pyogenes*, an organism of exceedingly variable virulence.

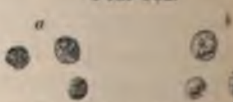
Pus, from a simple abscess occurring in an otherwise healthy person, is a thick, creamy, opaque, yellowish-white, slightly viscid fluid, having a faint odor, an alkaline reaction, and a specific gravity of 1030 to 1033. It contains ten to fifteen per cent. of solids, of which two-thirds are proteid, and the rest fatty matter and salts, such as are found in blood. On standing, it separates into a dense yellow layer, *pus-corpuscles*, and a clear supernatant fluid, *liquor puris*. Pus-corpuscles are for the most part dead leucocytes of the multinucleated variety. They are more or less granular and motionless: they usually contain a tripartite nucleus, which has not infrequently undergone degenerative fragmentation (Fig. 101). A small minority of the cells may be still living and retain their amœboid movements. These are the more recently migrated leucocytes. Acetic acid clears up the cells and renders obvious the often obscure nucleus (Fig. 102).

FIG. 101.

Multinucleated leucocytes from gonorrhœal pus. Two of them contain gonococci. × 1000.

On rare occasions, if all the bacteria be destroyed, a collection of pus may become encapsuled by the uniform development, round the fluid, of granulation-tissue and its subsequent change into fibrous tissue. Such pus may long remain encapsuled, its corpuscles breaking down into fatty débris; but, as a rule, the fluid part is absorbed, and a more or less dry, cheesy-looking mass, consisting of cell-débris and cholesterin crystals, is left in the capsule. This termination is most commonly met with in the so-called *chronic abscess* of tuberculosis.

FIG. 102.



Pus-corpuscles as seen in the urine. *a*, before, *b*, after, the addition of dilute acetic acid. × 400.

When a granulating wound is infected with pyogenic organisms, the superficial cells will be killed, the tissues liquefied and pus be formed on its surface, while the healing process will be consequently delayed. If the growth of the organisms be very abundant and extend into the underlying tissues, the same phenomena will occur as in the spread of an abscess, and the wound consequently become larger. This process is known as *ulceration*, which may be defined as progressive molecular destruction of tissue by irritant substances.

(6) **Proliferative Inflammation.**—In many cases, when the injury to the tissue has been slight but long continued, or when, from any cause, it has led to a considerable formation of granulation-tissue, the inflammatory process may end in the formation of a large amount of new fibrous tissue. Spindle cells develop around, and form the walls of, the capillary loops in the granulation-tissue (p. 167), and from these points gradually extend through the new tissue. White fibres seem to grow from the periphery of these cells, while the cells themselves shrink until little of them remains besides their nuclei. The new fibres also contract and many of the capillaries become obliterated. Under these circumstances, the inflammation is termed *productive* or *proliferative.*

The formation of this tissue is, as a rule, preceded by the usual vascular changes (p. 160) and by a slight emigration of leucocytes; and one of the most difficult problems in morbid histology has been, and still is, to discover how far the succeeding fibrous tissue is formed from the migrated leucocytes, and how far from the pre-existing connective-tissue corpuscles.

Among many important experiments which have been devised to solve this doubt, those of Sherrington and Ballance may be quoted. These observers constructed chambers, formed of two slightly separated circular cover-glasses with their edges cemented except at one spot, so that nothing could enter the space between the two cover-glasses except by the one small aperture which remained. These glass chambers were, with strictly aseptic precautions, placed in the subcutaneous tissue of dogs and were removed at varying periods. In some cases, in less than twenty-four hours after the cover-glasses were placed in position, leucocytes had entered in considerable numbers and had distributed themselves all over the enclosure. Only at the point of entry were there other cells—*plasma-cells*, or *fibroblasts*. These cells differed from the "pioneer" leucocytes in that they were larger, more coarsely granular, and possessed a single clear oval nucleus. In no case were transitional forms seen. The original leucocytes were never observed to undergo any but degenerative changes. The fibroblasts, on the other hand, showed greater power of amœboid movement and of enclosing corpuscles than the original leucocytes. It seemed evident that the fibroblasts were the *successors, but not the progeny*, of the leucocytes found in the earliest stages of inflammation. Sherrington and Ballance considered that the fibroblasts were one of the normal constituents of connective tissue. Metschnikoff maintains that fixed connective-tissue cells, endothelial cells, and the large uninucleated hyaline variety of leucocytes have alike the power of giving origin to fibroblasts, and,

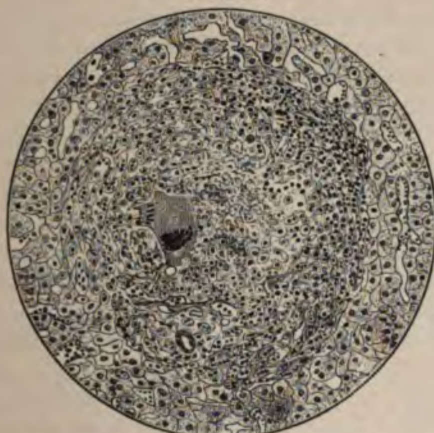
therefore, of developing into fibrous tissue. At the present time it is generally conceded that the fixed cells of the part—connective-tissue corpuscles and endothelial cells—take the principal share in the formation of cicatricial fibrous tissue, though it is possible that the large hyaline leucocytes (p. 178) also take some part in the process. In the tadpole, the formation of fibrous tissue from leucocytes has been observed.

The new connective tissue is called inflammatory or **scar-tissue**, and is precisely similar to that formed during healing by granulation (p. 167). At first it is highly vascular, just as a recent scar is redder than the surrounding parts; and the tendency to contract is also characteristic of this new fibrous tissue. It is useful as tending to draw the edges of wounds together, and thus facilitating the overgrowth of epithelium which finally covers in the wound. As this proceeds the vessels disappear, and the scar, in the course of some weeks or months, becomes white as compared with the surrounding parts. This *contraction* of scar-tissue may produce the gravest deformities, as after severe burns; or may, by pressure, cause atrophy of gland-cells and other parts, as in syphilitic cirrhosis of the liver. The contraction is most marked where the tissues are loose, as about the scrotum. It appears to be essential to the process of healing, for a callous ulcer of the leg will cease to heal if contraction of the new tissue be prevented by the infiltration of the surrounding tissues and their adhesion to deeper parts. A scar, and especially a tight scar, is always liable to secondary changes, such as *ulceration* or *overgrowth* (*cheloid*), and is a common seat of *epithelioma*. The tendency of scars is to disappear gradually.

Granulation-tissue does not always develop directly into scar-tissue. If some source of continued irritation, such as virulent micro-organisms, be present, or if the vascular supply be deficient, the process may be arrested or delayed, and degeneration follow. The normal healing process is dependent both upon the general health of the person affected and upon the local blood-supply: in conditions of physical exhaustion the granulation-tissue, owing apparently to defective nutrition of its cells, may fail to be converted into fibrous tissue, remaining soft, pale and gelatinous, and secreting thin seropurulent fluid. Owing to the failure of the normal process of contraction, such weak granulation-tissue may grow above the level of the surrounding parts, constituting "exuberant granulations"—the "proud flesh" of popular parlance. Deficient blood-supply may be due to insufficient development of vessels, diminution of their lumina (as occurs in gummata), or to pressure from too dense packing of the cells. It has been found that imperfect blood-supply is accompanied by the development of giant-cells; these are found in all chronic inflammations. A *giant-cell system*, such as is common in tuberculosis, consists of a giant-cell in the centre, surrounded by fibroblasts; while outside of these and intermingled with them is usually found a zone of leucocytes (Fig. 103). In gummata and lupus-nodules similar structures are

frequent. A section through the thickened synovial membrane in a case of chronic arthritis often shows the following appearances: externally, we find ordinary granulation-tissue, with some developing scar-tissue; passing toward the joint-cavity, we next find a layer of formative cells in which *giant-cells* become increasingly numerous, and even typical *giant-cell systems* may occur; nearer the joint, yellow spots and patches of fatty degeneration become frequent; and the surface may be composed of granular débris in which cell-forms are no longer distinguishable. A thin puriform fluid may occupy the cavity; it contains, however, very few pus-cells, but consists mainly of fatty granules —formed by degeneration of the superficial cells—suspended in an albuminous fluid. This is the change known as *chronic suppuration* of a joint. *Chronic abscesses* may form elsewhere, especially in connection with bone—*e.g.*, in caries of vertebræ. When starting from bone, the puriform fluid, formed by the degeneration of the granulation-tissue, presses upon and distends the surrounding tissues and

FIG. 103.



A tubercle from a case of tuberculosis of the liver. A multinucleated giant-cell occupies the centre. Around is an area of commencing caseation and, outside this, a zone consisting principally of fibroblasts, and, to a less extent, of leucocytes. The leucocytes are most numerous on the side where the caseation is most advanced. × 250.

converts them into a bag, the wall of which yields a little pus.

II. Explanation of the Phenomena.—We have now to seek the explanation of the various phenomena described under the six instances of the reaction of the tissues to injury.

Dilatation *of the bloodvessels with* **acceleration** *of the blood current* may probably occur in two ways. (1) Irritation of a sensory nerve is well known to cause dilatation of the arterioles in its own area of distribution. The action of an irritant not sufficiently intense to paralyze the vessels at once will stimulate the sensory nerves and cause this *reflex local dilatation* over a larger area than that mechanically damaged. The arterioles

dilate, and, the blood-pressure being maintained, a larger quantity of blood is admitted to their capillaries, which cannot dilate proportionately. The blood-pressure in the capillary areas is, *ceterus paribus*, raised in proportion to the increase in the cross-section of the supplying arterioles. Under these circumstances, acceleration of stream will accompany dilatation of vessels. The walls of the latter, being uninjured, may contract after such dilatation. (2) Cohnheim found that dilatation of the vessels in the frog's tongue followed irritation even after section of all the nerves, indeed of everything except the lingual arteries and veins. The dilatation may then be due to *direct action of the irritant upon the local vascular nervous system*, which maintains a certain "tone" in the vessels even after section of the sympathetic. Dilatation of arteries diminishes the resistance to the flow of blood, injury of endothelium increases it. If the former is in excess of the latter, acceleration of the blood-flow will occur. The acceleration is not seen in a part severely injured, nor as the result of the slow action of croton oil on a part. The acceleration is most marked in the outlying parts of the inflamed area.

Dilatation *of the bloodvessels with* **retardation** *of the blood-current.*—Retardation soon follows upon acceleration, though the driving force continues unaltered, and no contraction of vessels has occurred.

That this retardation is not due to any change in the blood is absolutely certain, for (1) not only do the corpuscles behave in a perfectly normal manner just before they reach, and directly after they leave, the affected area; but further (2), if the blood be replaced by milk or other fluid, before the inflammation is induced, precisely the same dilatation and retardation will occur. Almost the only conceivable cause of slowing is, therefore, increased local resistance, due to alterations in the vessel-wall. We know that in inflammation the endothelial cells swell, throw out processes and exhibit phagocytic powers. Owing to the necessary molecular changes the cells may become more sticky, or may present a rougher surface, and thus give rise to increased friction. The rapid passage of fluid out of the vessels may also assist in delaying the blood-stream. Our knowledge concerning the cause of dilatation and retardation is still very imperfect. Both of these phenomena may depend in some measure on the chemical influence of the same substances that attract the leucocytes into the surrounding tissues (*chemotaxis*, p. 179).

Exudation of Fluid.—To show this, Lassar tied a canula into a large lymphatic of each hind leg of a dog. He then stopped the circulation in *one* leg, and dipped this into hot water (130° F.), thereby exciting acute inflammation. On removing the obstruction the lymph-stream from the canula at once exceeded the normal, and soon reached *eight times* that on the sound side. At first the fluid was clear, but after a time increasing numbers of white corpuscles made it cloudy, and red corpuscles were also found in small numbers. Swelling of the foot began while the flow of lymph was free, evidently because the exudation was too rapid to be conveyed away by the lymph-channels alone, even when fully dilated. Later in the experiment the flow diminished,

partly because exudation diminished as pressure on the vessels (from effusion beneath the skin) rose, and partly from coagulation in, and consequent blocking of, lymphatics. The lymph collected differed from the exudation fluid in passive hyperæmia in containing a much larger proportion of proteid, and in having a much greater tendency to coagulation. This latter property varies with the number of white corpuscles which it contains. The lymph in Lassar's experiment differed from liquor sanguinis in containing less proteid and having a slighter tendency to coagulate. *The composition of inflammatory effusion, however, is not constant.* In the most acute inflammations it contains a large number of red corpuscles; in less severe forms white corpuscles are greatly in excess of red. In the more acute inflammations the fluid approaches plasma in its composition and tendencies; while in the less severe it becomes very like the fluid which exudes in passive hyperæmia. It also varies according to the part from which it comes. A mild degree of *peritoneal inflammation* will produce an effusion containing a larger proportion of proteid than a far more severe *inflammation limited to the leg* (p. 204). Inflammatory exudation is generally coagulable. Absence of coagulation may depend on the action of some restraining substances, such as albumoses, or on the solution of the fibrin by some ferment.

The increased exudation is attributed to an increased permeability of the vessel-wall and, to a less extent, to changes in the capillary pressure: the latter is a doubtful factor.

FIG. 104.

Inflammatory œdema of skin. The large spaces shown were filled with the exuded fluid. × 2½. (Boyd.)

The exudation in an internal organ gives rise to distention; in the subcutaneous tissue, to œdema (Fig. 104); on a mucous surface, to a sticky fluid containing mucin, or to a firm fibrinous layer on, and sometimes in, the lining membrane; on a serous surface, to a thin serous fluid, a fibrinous deposit, or a purulent accumulation.

The result of the exudation is to flush the part, thereby diluting and often distributing the irritant—the first a beneficent, the second a baneful, effect. The exudation has also an antagonistic chemical effect on bacteria, due largely to the products of the disintegrated leucocytes which it contains. (See *Immunity*.)

Emigration of Corpuscles.—It has already been pointed out that the escape of *red corpuscles* is a purely passive process, and is practically of the same nature as an ordinary hemorrhage. With regard to the *leucocytes*, the process is more complicated, and it is necessary to distinguish between the parts played by the different kinds. There are many classifications of leucocytes: that proposed by Kanthack and Hardy is a convenient one, and will be adopted here. According to these observers, the colorless corpuscles may be divided into the six following varieties.

(1) *Lymphocytes*.—These are small immature leucocytes formed in

the lymphatic glands. They consist mainly of a nucleus with a small encircling mass of protoplasm; they do not possess amœboid movements, and are not phagocytic (p. 179). They form about thirty per cent. of the total number of leucocytes.

(2) *Hyaline Leucocytes.*—These are large uninucleated cells with clear protoplasm. In the lower animals they are frequently met with in the cœlomic fluid; they possess amœboid movements and are phagocytic. In the blood they rarely form more than 2 per cent. of the total number.

(3) *Coarsely Granular Oxyphile Leucocytes.*—These are the *eosinophile cells* of Ehrlich. They have a large nucleus—often kidney-shaped or horseshoe-shaped. The protoplasm is highly refractive, and contains coarse granules staining with eosin and other acid* aniline dyes. They possess amœboid movements, but are not phagocytic. They are almost as rare in the blood as the hyaline cells, seldom exceeding 4 per cent. They are generally the first cells to appear in an inflamed area, and are probably identical with the wandering cells normally present in connective tissue.

FIG. 105.

Leucocytes from normal blood. *a*, lymphocyte; *b*, hyaline leucocyte; *c*, coarsely granular leucocyte; *d*, finely granular leucocyte.

(4) *Finely Granular Oxyphile Leucocytes.*—These are the *neutrophile cells* of Ehrlich, and are generally known as the *multinucleated leucocytes*, although the nucleus is really a single body consisting of three lobes or branches. The protoplasm is finely granular. The cells are amœboid and phagocytic. They generally form between 50 and 60 per cent. of the leucocytes in the blood. Pus-cells consist almost wholly of these leucocytes.

(5) *Coarsely Granular Basiphile Leucocytes* (*Mast-cells*).—These correspond in their appearance, habitat, and non-phagocytic properties with the third variety, differing only in their staining affinity and larger size.

(6) *Finely Granular Basiphile Leucocytes.*—These correspond in the same way with the fourth variety but are somewhat smaller. They form less than 5 per cent. of the total number of leucocytes.

The power of amœboid movement ordinarily possessed by leucocytes is sufficient to enable them to leave the blood-stream and to find their way into the tissues in inflammation. That the process of emigration is not a passive one is shown by the facts (1) that these corpuscles pass out long before any others; (2) that their amœboid movements may be

* By an *acid* dye is meant a salt in which the staining property is due to the acid radicle, and, conversely, by a *basic* dye, a salt in which the dye is associated with the base.

observed both before and after they leave the vessels; (3) and that, although absolute cessation of the circulation generally causes arrest of diapedesis, in some cases (tadpole) this is not so.

We have, however, still to inquire (1) why leucocytes collect in the vessels of an inflamed area; (2) why they tend specially to pass out at that place; and (3) what is the result of their emigration.

(1) It has been proved experimentally that, if the velocity of the circulation be gradually reduced, the leucocytes and the blood-platelets are the first constituents of the axial stream which tend to fall into the periaxial. It is uncertain why this occurs. That it is not due to the low specific gravity of the leucocytes seems clear; for if their specific gravity be artificially increased, by the ingestion of particles of vermilion, the tendency to margination is in no way affected. Once in the periaxial stream, itself moving at a slower rate than the axial, the leucocytes, rolling along the side of the presumably roughened wall of the vessel, will naturally tend to lag behind. Probably the principal force causing their detention in the periaxial stream is the same as that which attracts them through the walls of the containing vessels.

(2) It is well known that the mere presence of particles of metallic copper in the tissues of a part (anterior chambers of the eye) will cause leucocytes to collect in the neighboring vessels, to pass through the vessel-walls, and to approach the seat of the metallic particles. This attractive power is known as *chemotaxis*. It seems to be possessed by the diffusible substances produced by most pathogenic bacteria during their growth in the tissues.

There are two groups of experiments which are capable of explanation on this hypothesis. In the *first*, various organisms and chemical substances have been introduced into the tissues—generally in glass tubes, subsequently broken *in situ*. As a result, various degrees of inflammation and consequent diapedesis have occurred, certain organisms leading to the aggregation of special kinds of leucocytes. In some instances the subsequent introduction of some other substance has, by its repellent action, arrested the emigration already in progress (*negative chemotaxis*). Thus Metschnikoff has shown that if a frog's mesentery be moistened with a solution of quinine no diapedesis will occur, though, from their subsequent behavior, it can be shown that the leucocytes are not paralyzed. By the *second* group of experiments it has been shown that, if substances possessing a positive chemotactic influence be introduced into the circulation and subsequently into the tissues, their usual effect will by this means be neutralized and no emigration result. It seems to follow, therefore, that the aggregation and emigration of leucocytes at an inflamed spot are due to the attractive influences of certain substances existing in greatest quantity in the part to which the corpuscles make their way; while the vascular changes, including the dilatation of the vessels, the lowered rate of the blood-stream, the margination of the leucocytes, and the changes in the vascular endothelium, are mainly due to the action of the same substances and are valuable accessories in the process of diapedesis.

(3) Attention has already been directed to the observation that the coarsely granular uninucleated eosinophile leucocytes are the first to appear in a suppurating area. Though these have no power of phagocytosis, they have been observed to apply themselves to bacteria and to discharge their eosinophile granules, while the bacteria, thus brought into contact with them, degenerate. It has, therefore, been inferred that these leucocytes have some secretory properties. In the process just described some of the leucocytes are destroyed, and it is, therefore, also possible that the products of their disintegration may possess bactericidal properties. This is confirmed by the observations (1) that leucocytes contain a nuclein which is known to be a bactericidal substance, and (2) that inflammatory exudations are, in general terms, bactericidal in proportion to the number of leucocytes they contain. (See *Immunity*.)

While it seems tolerably certain that the leucocytes, by their secretion and by the products of their disintegration, exert an inimical action on at least some forms of bacteria, it is still more unquestionable that this is not the only defensive power possessed by leucocytes. It has long been shown that foreign substances entering amœbæ may be in some cases digested by them, and in others may lead to their death. It has been shown by many recent observers, but especially by Metschnikoff, that the hyaline and multinucleated leucocytes also possess the same power of taking into their interior living bacteria and of thus destroying them (*phagocytosis*). The greater the virulence of the bacteria the less marked is this power of the leucocytes, and the less rapidly is it exercised. Moreover, the power of reaction on the part of the leucocytes is subject to variation, for cultures of similar virulence do not produce the same results in all individuals belonging to the same species. In this way the multinucleated and hyaline leucocytes are enabled to combat and destroy living bacteria, as well as to remove dead and degenerating products of cell-action. It would seem that the different kinds of leucocytes are attracted by different substances, for in effusions (pleural, cerebro-spinal) produced by the tubercle-bacillus lymphocytes predominate, whereas in those due to pyogenic bacteria multinucleated leucocytes are found.

If the leucocytes are not attracted to the seat of the bacteria, neither their chemical nor phagocytic action will come into play; and, unless some germicidal influence is exerted by the tissues, the bacteria will multiply and become disseminated, giving rise to generalized disease.

Clinical Signs of Simple Inflammation.—These are, *redness, heat, swelling, pain, tenderness, and impaired function.*

Redness and *heat* may be considered together, as they both depend upon *the quantity of blood passing through the part* in a unit of time. As a rule, this quantity of blood is increased, the excess being most marked in the early stage of the process, when the part is bright-red and hot. While most of its vessels are dilated, the velocity of the blood-stream through them is not appreciably delayed; but as retardation supervenes, the quantity of blood passing through the part is diminished. Cohnheim excited inflammation in one foot of a dog, and

then measured the blood returning through both femoral veins. At first the delivery from the injured side was excessive, sometimes more than twice the normal; but when diffuse suppuration or sloughing was induced, and the circulation in a large area consequently delayed, the delivery became markedly less than normal. *Such a part is colder than normal*, and *bluish* if its vessels are dilated and full, but *mottled* or *pale* if they are compressed by exudation. In most inflammations the increased circulation in the outlying vessels is more than sufficient to compensate for the retardation and stasis in the most injured parts; consequently, the delivery from the veins remains excessive throughout, and the part is red and hot. Both redness and heat may be concealed if normal tissues cover the inflamed part. The skin of an inflamed foot may appear to be several degrees hotter than that of its fellow, but its temperature will never equal that in the rectum. An inflamed pleura is never any hotter than its fellow, and may be colder. The local rise of surface-temperature is due merely to more rapid circulation of arterial blood; excess of heat is not produced in an inflamed part.

Swelling, beyond the most trivial, which may be due to dilated vessels, is the result of *exudation of fluid and corpuscles*. It may be entirely owing to fluid, as in hydrocele; or entirely owing to small round cells, the fluid having been absorbed, as in orchitis. It varies in amount with the distensibility of the part, being most marked in such tissues as the scrotum and eyelids, and least marked in bone. When due to fluid (*inflammatory œdema*) the affected part "pits" on pressure, unless it is very tensely stretched. Swelling from cell-infiltration is firm, does not pit, and is sometimes called *solid œdema*. In cases of slight inflammation, in which the lymphatics suffice to carry away the increased exudation, there may be no perceptible swelling.

Pain and *tenderness* are due to *pressure* of the exudation *on nerve-endings*, perhaps also to *chemical irritation* of them. They vary directly with the sensitiveness and the tension of the part, as well as with the rapidity of the effusion into it, as is seen in acute suppuration in a digital tendon-sheath. Pain is often throbbing from the increase of tension produced by each heart-stroke. The influence of increase of pressure in producing pain is well shown by allowing an inflamed part to hang down.

Impaired function is due to the fact that every inflamed tissue is injured. The degree of impairment is proportional to *the damage done to the essential cells* of the affected part.

Fibrosis.—Reference must be made at this place to the origin of the fibrous overgrowth which is frequently met with in many organs of the body.

It was formerly assumed that all such fibrous tissue was inflammatory in origin—the result of long-continued slight irritation—and that the atrophy of the gland, muscle, and nerve-cells, respectively associated with it, was due to the contraction of the cicatricial tissue thus formed. But in the case of the nervous system there are strong reasons for believing that the atrophy of the nerve-elements precedes the development of the fibrous tissue, and is due either to defects in the blood-supply, or

to the direct action of such poisons as syphilis and alcohol. That the fibrous growth is not inflammatory in its origin is clear from the facts, (1) that it is exactly limited to the definite nerve-tracts and shows no tendency to spread beyond them, or to follow the distribution of the blood or lymph vessels; (2) that it is extremely gradual in its growth; and (3) that it follows the experimental destruction of the higher parts of the central nervous system. The fibrous overgrowth in such cases is probably due to the increased vascular supply available for the skeletal tissue after atrophy of the nerve-elements, though it is possible that the products of the degeneration of these cells act as irritants to the connective-tissue cells and stimulate their growth; but to some extent it is more apparent than real, and due to the increased concentration and visibility of the pre-existing connective tissue, which necessarily follows the shrinking of the atrophied parts.

On the other hand, many forms of fibrosis are clearly inflammatory. Thus the cicatricial tissue succeeding granulation-tissue in wounds, enclosing parasites and infarcts, or occurring in gummata and tubercular lesions, forms the final stage of inflammatory processes.

The position of the fibrosis occurring in the liver (cirrhosis) and the kidney (granular contracted) is still disputed, and will be referred to when these diseases are described. Adami considers that non-inflammatory fibroses are due to the effect on pre-existing fibrous tissue of (1) increased arterial supply, (2) venous congestion, and (3) lymphatic obstruction.

III. Varieties of Inflammation.—It has been shown that necrosis and degeneration form the earliest changes in the tissues, and that repair and regeneration, always more marked in the connective and least organized tissues, form the final stage. Between these, in point of time, when vascular tissues are involved, are the series of changes in the vessels and surrounding tissues involving various disorders in the circulation, but especially a marked emigration of leucocytes and still more marked exudation of fluid. These various phenomena—damage, exudation, repair—do not exist in the same proportion in every instance of inflammation. Sometimes the necrosis and degeneration are very marked, while the vascular changes and the subsequent repair are comparatively slight. In other cases, particularly when surfaces of tissue are affected, the exudation of fluid and the escape of leucocytes are the principal changes. In other examples, especially where the connective tissues are involved, the proliferation of existing tissues is more marked than the degenerative or the vascular phenomena. For these reasons Leber has suggested a useful classification of inflammation into three varieties: (1) *degenerative*, as in acute parenchymatous nephritis; (2) *exudative* or *infiltrative*, of which suppuration is the best example, but which also includes catarrhal, croupous, diphtheritic, serous, fibrinous and all acute forms of "surface" inflammations (see *Diseases of Mucous and Serous Membranes*); and (3) *proliferative*, of which verrucose endocarditis may be, according to Leber, taken as the type. The difference in the character

of the inflammation depends partly on the tissue affected, and partly on the nature of the irritant at work. Examples of the different forms will be found in the sections dealing with the diseases of special organs.

IV. Etiology of Inflammation.—As in the case of other morbid conditions, there are two factors in the inflammatory process, (1) the *irritant* and (2) the *tissues* upon which it acts. The causes of inflammation are, therefore, divisible into **exciting** and **predisposing**. Sometimes the exciting cause is so powerful that no special predisposition is necessary; but not infrequently the exciting cause only gives rise to inflammation when the resisting power of the tissues to the irritant in question has been lowered. This impairment of resisting power is the work of the *predisposing* causes, and it may be either inherited or acquired (p. 19). It is obvious that, in cases where predisposition is necessary, the condition of the tissues is as essential to the production of an inflammation as is the presence of the exciting cause itself: the seed and the suitable soil are alike necessary to produce the plant.

With regard to the nature of the exciting cause or irritant, it is always some chemical, mechanical, or other physical agency. Simple deprivation of blood-supply, leading to the formation of injurious products of disordered metabolism in the surrounding tissues, is enough. If the exciting causes be of sufficient strength and be continued for a sufficient time, they cause actual necrosis of the part; and inflammation is limited to a narrow margin of the living tissue at its line of contact with the dead.

Difficult as it is to discover the cause of many inflammations, we should bear in mind the very obvious fact that *no inflammation ever arises without a cause, simple or complex. A spreading inflammation is due to a spreading cause; and a persistent inflammation (chronic) implies the persistent action of its cause.*

1. Simple or Traumatic Causes.—These include any very evident injurious agencies, such as mechanical violence, caustic and irritating chemicals, excessive heat or cold, electricity strong enough to produce electrolysis of the fluids of the part, and prolonged local anæmia with consequent privation of nutriment. It is characteristic of inflammation from these causes alone, that it has *no tendency to spread beyond the part originally injured nor to pass on to more advanced stages after the causes have ceased to act.* It is well known how slight are the inflammatory changes induced by very severe *subcutaneous* injuries, even though bones be broken and the capsules of joints torn; and how limited is the inflammation when similar injuries, *communicating with the atmosphere* (*e. g.*, compound fractures) are treated in such a way (antiseptically) as to exclude all infective causes. In animals the effects of each of these irritants can be accurately studied. Hüter injected a 5-per-cent. solution of nitrate of silver, or a similar solution of chloride of zinc, into the muscles and other tissues of animals, and thus killed the part acted on. In a large number of the cases the inflammation was practically limited

to the zone immediately surrounding the dead tissue. Other experiments were made by plunging a cautery into a muscle (Hallbauer) and bringing the previously divided skin together over the injured part, antiseptics being used. Only such changes occurred round the eschar as take place in the absorption of a simple infarct and its replacement by fibrous tissue. Here, then, we have examples of the most severe mechanical, chemical, and physical injuries killing considerable masses of tissue. In each case the action of the irritant, though intense, is localized and of short duration. Certain parts are killed absolutely, and inflammation is limited to a narrow area surrounding these. So soon as the irritant has ceased acting, the tissues tend of themselves to recover; hence inflammation excited by such causes as the above reaches its height very soon after the introduction of the irritant, and soon subsides unless some fresh irritant is superadded. This is frequently seen after the infliction and proper treatment of a clean-cut wound by a sharp knife (p. 164). A chemical irritant may enter the body at a distance from the part at which its chief action takes place: thus alcohol taken by the mouth is concerned in the production of cirrhosis of the liver; and turpentine or cantharides may in the same way cause inflammation of the kidneys.

In this group come inflammations which are referred to cold and wet—"rheumatic" and "reflex" inflammations. When a man gets conjunctivitis from the action of a draught upon his eye, the relation between cause and effect is easily comprehensible; but, except on the hypothesis of greater delicacy of nerve-tissue, it is not quite so easy to understand why inflammation of the facial nerve should ensue from exposure to cold, whilst a great thickness of superficial tissue seems uninjured. But this difficulty becomes much greater when internal organs (lungs, kidneys) become inflamed, apparently in consequence of cold acting upon the surface, or of wet feet. In these cases any effect produced by cold may generally be regarded as predisposing. We know that surface-cold drives the blood to internal organs and raises the blood-pressure. Can this produce inflammation? Lassar plunged rabbits, shorn of fur, into iced water and thoroughly chilled them; he found changes in all the organs, especially the lungs and liver. In these the vessels were often greatly dilated, the arteries thrombosed, and the veins surrounded by patches of round cells. When the animals were pregnant, the same changes were noted in fœtal organs. He believed the changes to be due to the irritant action of cooled blood upon the vessels of internal parts. Perhaps something of the same kind may occur in man, as the result of a chill, although a *locus minoris resistentiæ* or the presence of organisms must be assumed to explain why the kidney in one case, and the lung in another, is affected. Frequent exposure to cold might then be regarded as a cause of chronic nephritis; for the temporary albuminuria induced in some people by a cold bath shows that in them the kidneys may be easily damaged.

It is held by some that *excessive functional activity* is a direct cause of inflammation—conjunctivitis from overwork being the usual example.

Nervous influence, called into action by irritative lesions of nerve-trunks, appears capable of directly causing a process resembling inflammation. The most striking instance of this is seen in herpes zoster, in which a cutaneous inflammation, manifested by an erythematous and vesicular eruption, is associated with neuralgic pain and with changes in the cells of the posterior-root ganglia corresponding with the nerves going to the affected area of skin.

2. Infective Causes.—In a very large number of the inflammations met with in practice there has been no obvious mechanical, chemical, or physical injury. In the chapter on vegetable parasites, evidence will be given to show that many of these inflammations are due to the action of fungi. The growth of these organisms in the tissues gives rise to mechanical and chemical irritants, producing inflammation in the same way as do the agents which have been mentioned as causes of simple inflammation. But, as long as the fungi grow in the body, a *continuous* supply of the products of their life-action is kept up. These products, continuously spreading through the tissue, will accordingly give rise to a spreading inflammation. The products of different fungi vary enormously in their power of injuring the tissues—some producing actual necrosis, others, varied degrees of inflammation. If the irritant is sufficiently intense, some variety of fibrinous inflammation is induced, just as by chloride of zinc; when a strong irritant produces a proteolytic ferment, and exerts positive chemotaxis on the leucocytes, suppuration results. If the irritant is less intense, the early stages of proliferative inflammation result, as in tubercle and leprosy. The characteristic lesion of these and some other diseases is a tumor-like inflammatory nodule developed round a spot at which parasites have lodged, and whence they may spread and infect neighboring and distant parts. Diseases characterized by these lesions are, therefore, often spoken of collectively as the *infective granulomata*, a name signifying infective, tumor-like formations of granulation-tissue.

It would, however, be a great error to suppose that the *presence of organisms* capable of producing irritant products is invariably sufficient to cause inflammation. We have already pointed out that the *resistance of the tissues* must always be taken into account; moreover, the rôle of organisms in the production of inflammation will be influenced by their detention in the tissues, by any local lesion or predisposition in the tissues, by the anatomical characters of the part, and other conditions. These subjects are discussed in Chapter IX.

Etiology of Suppuration.—In clinical medicine and surgery suppuration is invariably due to the action of bacteria (p. 170), but there is reason to believe that suppuration is possible in experimental pathology without the action of organisms. If glass capsules, containing croton-oil or turpentine, are placed aseptically in the subcutaneous tissue, and the capsules broken when the wound is soundly healed, suppuration results, and no organisms are found in the pus (Cheyne, Councilman). Grawitz and Scheuerlen have produced acute aseptic (free from organisms) suppuration by the injection of cadaverine and putrescine—alka-

loids, separated by Brieger from putrid flesh. These substances are not only irritants, but also possess proteolytic (peptonizing) powers.

Modes of Spread of Inflammation.—An inflammation which is characterized by a tendency to spread will always be found to be of parasitic origin. Clinically, inflammations spread by continuity of tissue, by the lymphatics, or by the blood-path. *Micro-organisms*, having settled at a spot, can spread thence, very much as is the case with malignant growths. (1) They may push their way along the paths of least resistance as they grow, or be carried for short distances by the exudation from the vessels, by the ordinary lymph-streams, or by leucocytes which have taken them up—spread of the inflammation by "continuity of tissue" resulting in each case. (2) They may be carried by the lymph-stream long distances from the primary focus. Conveyed in this way, they are usually arrested in the first lymphatic gland they reach. Here they often excite a secondary inflammation without having caused any trace of inflammation *between* the primary focus and the gland—the organisms passing easily through the lymphatic vessels, but becoming arrested in the sinuous channels of the gland, precisely like the particles of pigment which may be found, upon microscopic examination of a gland, on the "central" side of any extravasation of blood. (3) The organisms may enter the bloodvessels and be carried about by the blood-stream until arrested, when, under favorable conditions, they will multiply and give rise to a secondary (metastatic) inflammation, such as occurs in pyæmia in almost all organs or parts, and in mumps when the testis or ovary becomes inflamed.

Modes of Arrest of Inflammation.—The cessation of inflammation excited by one of the *simple* causes is brought about by *removal or encapsulation* of the cause. (1) *As soon as the causes are removed, the cells of the damaged tissues begin to exert their inherent tendency to recover from injury* (p. 21). Dead and dying cells are, in most cases, removed by leucocytes, and washed on by the exudation from the vessels; later on, their places are taken by new cells springing from the normal tissue-elements. (2) When the irritant cannot be removed, as in the case of some foreign bodies and animal parasites, it may become enclosed by a firm envelope of cicatricial fibrous tissue and its effects thus neutralized. This process is known as *encapsulation*.

When once *bacteria* have gained a foothold in the tissues and have begun to multiply and spread, the process is obviously more difficult to check. Clinically, inflammations spread rapidly and widely, and yet, even after causing gangrene of a large part of a limb, may become ultimately arrested. All the time there is a struggle for existence going on between the cells and fluids of the body on the one hand and the invading parasites on the other. The victory may lie with either, being won, sometimes easily, sometimes after a struggle of which the issue is for a long time doubtful.

Definition of Inflammation.—In the foregoing paragraphs the term "inflammation" has been retained in accordance with custom, and the process has been treated as if it constituted a distinct pathological condition. It is evident, however, that the phenomena seen after simple destruction of some cells of the cornea, and those resulting from injury to a portion of the skin, differ from one another merely owing to the presence of bloodvessels in the latter part: all the special features of the cutaneous lesion—hyperæmia, exudation, and the rest—result from the action of the irritant on the vessels and their contents. Secondly, it is clear that the phenomena occurring after a simple aseptic incision into the skin are essentially the same as those which are present when "inflammation" of such a wound occurs; the phenomena of what is clinically called "inflammation" differ only in degree and duration from those of conditions in which there is no such occurrence.

We are thus in the presence of an obvious difficulty: either the term "inflammation" must be extended so as to include healing of an aseptic wound by first intention—a condition to which it was specially intended to be opposed—or we must limit the use of it to certain instances in which the phenomena described occur with marked intensity, excluding cases which differ only in degree and not in kind. We have, in short, to admit that inflammation is a clinical term applied to a group of symptoms only arbitrarily separable from those of simple reaction to injury, and that the term does not admit of accurate definition in pathological language. For descriptive purposes it may be roughly defined as "the reaction of a living vascular tissue to continued or repeated irritation."

Since, then, inflammation is a clinical and not a pathological term, it is useless to inquire whether it includes repair of injury, or only the changes which precede repair—a question around which much controversy has centred. It is evident that the object of the process is defensive.[1] The vascular reaction leads to effusion of fluid which dilutes the poisons responsible for most instances of inflammation, and also facilitates the assemblage of leucocytes at the point of injury, carrying with them substances antagonistic to invading bacteria, and ready to devour the germs themselves; later the connective-tissue cells multiply and fill the gap left by the death of those which have been killed by the irritant, and thus repair is effected. These cells are partly stimulated to multiply by the action of the original irritant; partly, in all probability, they increase through diminished surrounding resistance, owing to the death of neighboring cells, and partly as a result of the increased blood-supply which exists in an inflamed part.

[1] According to the evolutionary theory upon which all biological science is now based, animals which reacted to injury in such a way as to counteract that injury would survive; those which reacted otherwise would die out. Hence a process favorable to the survival of the organism would tend to be perpetuated. Accordingly, it is legitimate from this point of view to "explain" a vital phenomenon in terms of its object or "final cause," although such an explanation does not assist in elucidating the mode in which the phenomena are brought about.

REPAIR OF SPECIAL TISSUES.

The power which most tissues possess of repairing losses of substance has been alluded to. We must now briefly state how such losses are repaired.

There are certain general statements that may be affirmed of the process of regeneration.

(1) A tissue can only be regenerated by the growth of a tissue of the same kind. It is well known that the cells of one embryonic layer never produce tissues other than those which normally develop from this layer; and it is also true that regeneration of a tissue occurs only from cells of that tissue—*e. g.*, muscle from muscle, epithelium from epithelium. The only exception to this is that any kind of connective tissue may be formed from any other kind.

The regenerative processes which ordinarily go on in adult mesoblastic tissues are still imperfectly known. Their reproductive energy has been supposed to be limited to molecular repair. Nevertheless, it is certain that the cells of most adult tissues retain the power of multiplication. That this is not manifest under normal conditions is possibly because the blood-supply received by the tissues is only sufficient to maintain the *status quo*, while the resistances opposing growth, such as pressure within tissue, are equal to the force with which they tend to multiply. If, however, the intercellular pressure be lessened by wound or by destruction of tissue, absorption of the damaged elements and multiplication of the cells round about will begin. Such injuries usually increase the blood-supply.

(2) The tendency of a tissue to regenerate varies with (i) the *age* of the tissue, all tissues being more easily regenerated in fœtal and early life than later on; (ii) with the blood-supply (p. 86); and (iii) with the kind of tissue, the more highly specialized the tissue the less readily does regeneration take place. Complex tissues are often temporarily repaired by an overgrowth of their connective-tissue stroma.

The multiplication of cells in repair, as in normal development, generally takes place by the division of one cell into two, the nucleus first dividing by the process known as *karyokinesis* or *mitosis*. The process in no way differs from that described in normal histology.

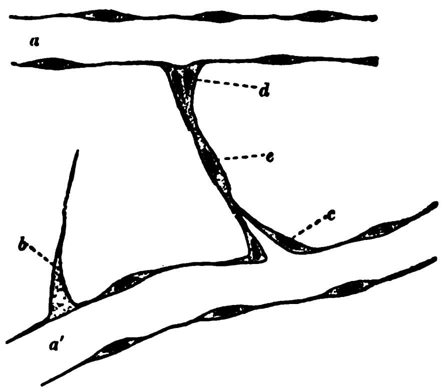
On rare occasions *mitotic division of the nucleus into three or more segments* may take place, or *direct division of the nucleus and cell* occur without the nuclear changes just described (*amitotic division*). In other cases so-called *fragmentation of the nucleus* may occur, in which the nucleus alone subdivides with or without any increase in the chromatin. This is one possible method by which giant-cells may be formed.

Connective Tissue and Bloodvessels.

Connective tissue, including vessels, may be derived (1) from the fixed connective-tissue cells, (2) from the wandering uninucleate plasma cells; and (3) from the endothelial cells of the vessels.

The repair of connective tissue has, however, already been discussed (p. 173): it is here only necessary to describe the formation of blood-vessels in detail. In post-embryonic life capillaries develop by budding.

Fig. 106.



Regeneration of capillary bloodvessels. *a*, normal capillaries; *b*, capillary process; *c*, new capillary appearing in divided process; *d*, process undergoing division; *e*, connecting-cell in which no sign of division has yet appeared. (Diagrammatic.)

By the end of the second day after the infliction of a wound, solid, pointed processes begin to project from some of the cells forming the walls of the capillaries: they increase in length and join similar processes from other capillaries, or, occasionally, processes of branched connective-tissue corpuscles. The processes are at first very fine but gradually widen, especially at the place where they join the fully formed vessels. Nuclei appear in these processes and then divide, complete cell-division following a little later. The lines of union of the individual endothelial cells, as shown by nitrate of silver, appear subsequently. In the mean time, channels are formed as the cells divide. These channels open into the original capillaries, and thus the blood-cavity becomes extended.

The new vessels increase in size with the demands made upon them. According to Thoma, the increase in the size of the vessels is in proportion to the rapidity of the blood-flow through them; while the thickness of the vessel-wall depends upon the tension of the wall—that is, upon the diameter of the lumen and upon the blood-pressure.

Muscular and fibrous coats are developed by direct extension from similar cells on the original vessels.

Epithelium.

Epithelium is always derived from pre-existing epithelium by mitotic division of the cells (Fig. 95). This is shown by the fact that it always spreads in from the edge of an ulcer, unless islets of the rete have been left undestroyed in the midst of the granulation-tissue, or unless accidental transplantation has occurred.

The *epithelium of the skin* and mucous membranes is readily destroyed and replaced throughout life, sometimes very rapidly, as in catarrhs of mucous membranes.

Glandular epithelium regenerates less readily. If all the cells in an acinus or in a tubule be destroyed, there is no reproduction of the epithelium therein. A wound of a gland, with or without loss of substance, heals by scar-tissue, which is permanent. Regeneration of *liver-cells* is known to take place in the dog, cat, and rabbit. Mitosis has also been observed in the *renal epithelium* of man. The regeneration of epithelium furnishes many illustrations of the rule that, the more highly specialized the function of a tissue, the less likely is that tissue to be capable of regeneration.

Regeneration of *nails* and *hair* is frequent. The structures are continually being formed ("growing") by groups of cells situated at their bases: destruction of these cells prevents further growth or regeneration of the hair or nail.

Muscle.

A *wound* in a **voluntary muscle** is temporarily repaired by fibrous tissue. As a rule, such a wound gapes widely and heals by granulation; but in some parts—*e. g.*, the tongue—retraction is prevented, and then union by first intention occurs readily.

When a muscle is incised, the protoplasm escapes through the opened sarcolemma, and leucocytes penetrate for some distance between the fibres. Granulation-tissue followed by ordinary scar-tissue is formed from the endomysium, and unites the ends of the muscle. New muscle-cells may then be produced by mitotic division of those on each side of the scar, and, later on, these may invade and eventually replace the cicatricial tissue. According to some observers, the surviving nuclei of the damaged fibres are sometimes able to multiply and form new fibres. In some cases, no regeneration of the muscle-cells occurs, and it is very rarely complete.

Degenerated fibres may be similarly replaced. This is seen in acute febrile diseases, especially typhoid fever.

Involuntary muscle-cells also multiply by division.

Cartilage.

A wound or breach in cartilage is generally repaired in the first instance by scar-tissue. This may be replaced later by hyaline cartilage formed from the perichondrium, and by proliferation of neighboring cartilage-cells. The matrix is formed, according to Strasser, from the protoplasm of the cells. Often the replacement of the scar-tissue by cartilage does not occur. In cases of fractured rib-cartilage the fibrous tissue may ossify into a clasp of bone round the broken ends.

Bone.

When a bone is broken, it generally happens that the encircling periosteum is partly, or completely, torn across, as well as separated from the broken ends for some distance above and below the fracture. The damage to the surrounding tissues is liable to greater variation. In any case, many bloodvessels will be ruptured, while the interval between the ends of the bone will be filled, and the rent in the soft tissues distended, by the resulting hemorrhage, which is finally arrested by the pressure of the extravasation and by the occurrence of thrombosis, as in healing by *first intention* (p. 164). If bacterial infection be prevented and the parts kept at rest, reparative changes commence in a few hours. The vessels undergo the usual changes characteristic of simple inflammation (p. 160), and large numbers of leucocytes infiltrate the damaged tissue and invade the blood-clot. The exact intervals between the appearance of the different changes, which next follow, vary with the size of the bone and the extent of the damage.

In general terms, the damage outside the periosteum is repaired by granulation-tissue and regeneration, as in the case of any aseptic wound; while, inside the periosteum, new tissue of a somewhat similar type is developed, mainly from the periosteum itself, forming a spindle-shaped swelling in which the broken ends of the bone are imbedded (Fig. 107). This tissue also grows between and connects these ends, forming the basis of the final repair. To a less extent, similar tissue is formed in the medulla. The new tissue thus formed round the bone and in the medulla is known as the *provisional callus*.

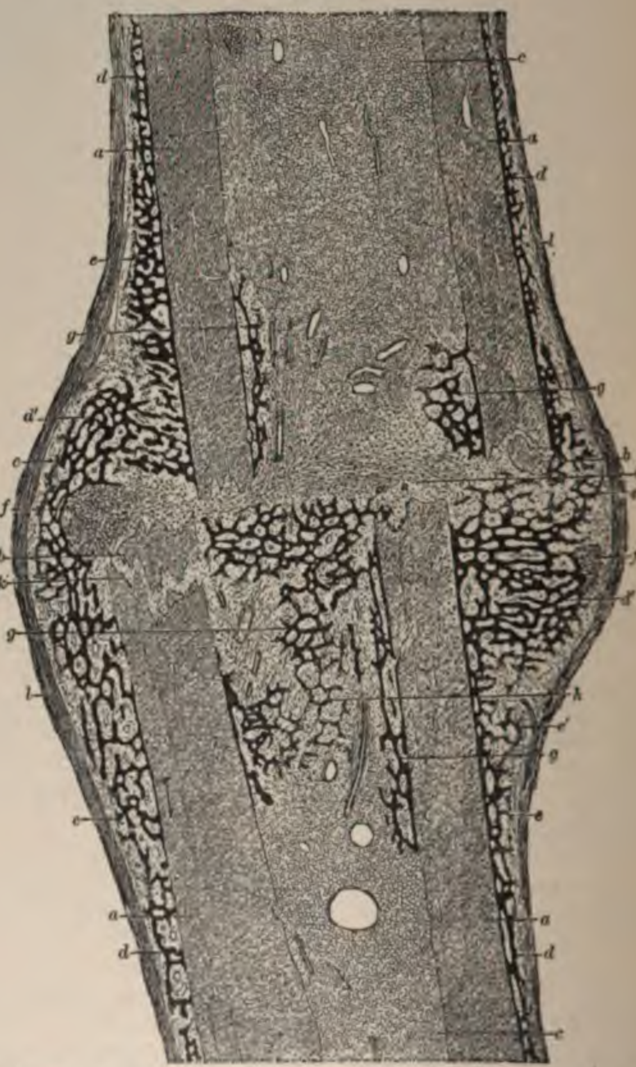
In the case of a bone like the fibula (Fig. 107), the cells of the separated periosteum and of the medulla begin to proliferate two or three days after the injury. By the latter half of the first week the innermost (osteoblastic) layer of the periosteum has produced a large amount of new tissue consisting of broad spindle-shaped cells, plentifully supplied with bloodvessels derived from the proliferating endothelium of those in the neighborhood.

Trabeculæ of osteoid tissue, and occasionally of cartilage, next appear in the new tissue in immediate contact with the stripped bone, and gradually spread until they occupy the whole space between the separated periosteum and the bone. By the end of the second week the extravasated blood and emigrated leucocytes have disappeared and the space between the fractured ends is bridged by osteoid trabeculæ with osteoblasts, fragments of cartilage, and strands of connective tissue. The osteoid trabeculæ, cartilage, and connective tissue are gradually transformed into bone, while the remnants of vascular granulation-tissue lying between the osseous trabeculæ come to resemble ordinary bone-marrow. The growth of the trabeculæ is more extensive between the periosteum and the bone than it is in the medulla. In the meantime the dead tissues including the sharp and jagged ends of the bones have been absorbed (p. 35).

The new tissue which actually connects the broken ends is derived

from the vascular, spindle-celled tissue developed from the periosteum: it is the last of the permanent tissue to appear and the last to undergo

FIG. 107.



Longitudinal section through a fracture of the fibula—fourteen days old. (From a man aged 25; preparation hardened in Müller's fluid, decalcified with picric acid, stained with hæmatoxylin and carmine, and mounted in Canada balsam. *a*, compact tissue of the fibula; *b*, small splinters; *c*, fatty marrow; *d*, *d'*, periosteal osteophytes; *e*, *e'*, trabeculæ of osteoblasts and osteoid tissue; *f*, newly-formed cartilage; *g*, myelogenous osseous trabeculæ; *h*, myelogenous trabeculæ of osteoblasts and osteoid tissue; *i*, connective tissue covering the fractured ends; *k*, osteoblasts; *l*, external fibrous layer of the periosteum. × 6. (Ziegler.)

final and complete ossification (*permanent* or *definitive callus*).

The first sign of involution is the removal of the jagged ends already referred to, and the absorption of any detached fragments of bone that may have died. When the ends of the bone are thoroughly united by firm compact tissue resorption of the callus begins. This generally commences in the third month after the injury. The more accurate the apposition of the ends, and the more correct the general position, the more complete will be the disappearance of the callus. So completely may it disappear that in a few months or years it may be extremely difficult to localize the exact position of an old fracture.

Repair of a fracture may be impeded by anything that causes undue movement of the fragments, by strands of muscle or other foreign tissue lying between the ends of the fragments, or by constitutional diseases which reduce the regenerative power of the tissues. If the fracture cause laceration of the nutrient artery leading to either fragment, the latter may undergo atrophy and exhibit no tendency to repair.

Nerve-cells and their Processes.—These will be referred to in the chapter on Diseases of the Nervous System (see *Index*).

Transplantation of Tissues.

Even before John Hunter's success in transplanting a cock's spur into its comb, it was believed that pieces of the body, like the tip of the nose or finger, might reunite if fixed in position soon after complete separation from the body; but accurate knowledge on this subject has been acquired only since Reverdin's discovery of "skin-grafting."

The tissues, as is well known, may survive systemic death for a short time. Portions of almost all tissues may be removed from one part or animal and successfully transplanted to another part or animal, if the conditions are suitable. These are: transference of the portion of tissue with sufficient gentleness and quickness to ensure that it is alive when transferred; close contact with the raw surface prepared for it; maintenance of its temperature; and the avoidance of all bacterial contamination. The piece of tissue will, under these circumstances, become united by *first intention* to its bed, and will be nourished by lymph transuding from this surface until vessels shoot across into it. Those tissues which are least highly organized and which require the least nutriment bear transplantation best.

Epithelium is the tissue which can most easily be transplanted. Use is made of this fact in the operation of grafting, in which small bits of *the superficial part* of the *rete* are placed upon a healthy granulating surface. At first, nourished by the exudation, these fragments grow, adhere, and form centres whence epithelium spreads over the surface. The cells of the root-sheath of plucked-out hairs answer the purpose well. Granulation-tissue may be covered with new skin in this way; but unless scar contraction accompanies the skinning-over, the cicatrix is liable to break down.

A piece of *skin* an inch square, freed from all fat, may be transplanted, and thus ectropion and similar deformities may be remedied.

Similarly, a bit of *mucous membrane*, usually obtained from a rabbit's conjunctiva, is transplanted in cases of entropion.

Cartilage and *periosteum*, especially when young, bear transplantation well (p. 99). So also do small pieces of *bone*. Macewen built up the shaft of a humerus with bits removed from deformed tibiæ, and introduced the practice of replacing, in the opening made in the skull by a trephine, chips of the bone removed.

Pieces of *muscle* have been successfully transplanted, and part of the sciatic *nerve* of a bird has been substituted for a corresponding piece excised from another bird. In *man* transplantation of nerve-lengths, taken from man and other animals, has been several times successful in restoring the function of divided nerves, even when months have elapsed between the injury and the operation. In all probability these nerve-lengths merely act as guides along which the regenerated axis-cylinders can grow.

CHAPTER VII.

LOCAL DISTURBANCES OF THE CIRCULATION.

THE efficiency of the circulation depends on the maintenance of a correct relationship between the action of the heart, the size and elasticity of the bloodvessels, and the quantity and composition of the blood, as well as on the preservation of a healthy lining membrane throughout the whole of the vascular tract. It is altogether out of the scope of this work to deal fully with the many ways in which these various factors may deviate from the standard of health. Practically, in disease, such lesions are nearly always combined. Structural defects of the heart, arteries, and veins, together with their results on the general circulation, will be dealt with subsequently. It is here only necessary to give a brief review of the causes and effects of *diminution* and of *increase* in the blood-supply of a part, and then to deal at greater length with the phenomena of *passive congestion*, *dropsy*, *thrombosis*, and *embolism*.

LOCAL ANÆMIA.

By *local anæmia* is meant diminution in the amount of the blood in a part owing to deficiency of the supply. It may be partial or complete.

Causes.—The causes of diminished arterial supply comprise all those conditions which either narrow or completely close the lumen of the supplying artery. The lumen of an artery may be diminished by disease of its walls—atheroma, calcification, or syphilitic thickening; or by pressure exercised upon it from without, by new-growths, constricting scars, inflammatory exudations and mechanical effusions, especially in unyielding tissues, such as bones or tendon-sheaths. Complete closure of the vessel may result from some of the foregoing conditions, or, more commonly, from thrombosis, embolism, or ligature. In some cases the supply of blood is diminished by an increase in the natural resistance, due to irritation of the vaso-motor nerves. This occurs in some neuralgic and other nervous affections (*Raynaud's Disease*), or from the action of certain substances, such as ergot of rye, or again, merely as the result of a low temperature. It is sometimes attributed to the presence in the vessels of products of metabolism, either in excessive amount or of abnormal character. Anæmia of one part may be secondary to hyperæmia of other parts, as, for instance, anæmia of the brain and skin in congestion of the abdominal viscera; or it may be due to a general diminution of the total quantity of blood, as after hemorrhage, in which case the parts most distant from the heart suffer most.

Results.—A part with a diminished arterial supply is usually paler, less tense, and of a lower temperature than natural. Its nutrition is defective; functions are impaired and it is liable to fatty degeneration, atrophy, or death. These results have been exemplified in the chapters on Fatty Degeneration, Atrophy, and Necrosis.

Obstruction of a large artery causes rise of pressure (transient under healthy conditions) everywhere except in its own area; and this increased pressure endangers the safety of delicate or diseased vessels, until the extra blood thrown into the suddenly curtailed vascular system is accommodated in some way. The heightened pressure affects the vaso-motor centre, and this speedily produces dilatation of vessels sufficient to restore the normal pressure. But the vessels which dilate most markedly and persistently are those going to the anæmic part and anastomosing with branches from the trunk beyond the obstruction (p. 218). These "collateral" vessels become larger, longer (tortuous), and thicker, until the circulation in the part has again become normal—*i.e.*, *collateral circulation* is established. At first, all vessels having anastomoses with the obstructed one probably dilate; but those which enlarge permanently are almost invariably branches on the same side as the obstruction—*e.g.*, the *right* inferior thyroid and vertebral arteries dilate after ligature of the *right* carotid. The primary anæmia, the blush and heightened temperature of vascular dilatation, and the final return to the normal, can be seen in limbs after ligature of main vessels.

HYPERÆMIA.

Hyperæmia, or *congestion*, is excess of blood in the more or less dilated vessels of a part. It may be (1) **active** (*arterial*) or (2) **passive** (*venous*). These two varieties must be considered separately.

ACTIVE OR ARTERIAL HYPERÆMIA.

Active hyperæmia means excess of arterial blood in a part, with, in most cases, acceleration of flow.

Causes.—The immediate cause of active hyperæmia is in all cases *diminished arterial resistance.*

Diminished arterial resistance may be produced pathologically—

1. *By certain agencies which have a weakening or paralyzing effect upon the involuntary muscle of vessel-walls.* *Fatigue* from previous prolonged contraction has this effect, as seen in the hyperæmia of the hands which follows snowballing. *Warmth*, too, is generally placed under this heading. *Injuries* of all kinds, apart from the reflex hyperæmia due to their effect on sensory nerves, cause dilatation by direct damage of the vessel-wall; and, so long as it is more than sufficient to counterbalance the increased resistance which always accompanies it (p. 176), the quantity of blood passing through the part is greater than normal—*i. e.*, the part is hyperæmic.

2. *By the removal, either directly or reflexly—i. e., by inhibition—of the vaso-tonic action of the sympathetic.* Thus, active congestion follows pressure by an aneurism upon the sympathetic in the neck. Certain drugs, taken internally, are believed to directly paralyze the vaso-tonic nerves—*e. g.*, nitrite of amyl, alcohol, tobacco.

The *reflex* process is generally due to stimulation of sensory nerves, the diminution in tonus thus produced being more or less accurately confined to the region supplied by the nerve. Friction and slight irritants in the early stages of their action produce hyperæmia in this way. It seems probable that vascular dilatation of deep organs may be produced reflexly by stupes and other applications to the skin over them, or, more accurately, to those portions of the skin in connection with the same spinal segments. Conversely, visceral disturbances may possibly give rise to vaso-motor changes in the corresponding cutaneous areas, or, indeed, in areas less limited than these; for Head has shown that in anæmia and other diseases the effects of such disturbances are less definitely localized.

Anæmia of any large part—as of a limb, compressed by Esmarch's bandage, or of the skin from cold—necessarily causes *hyperæmia* of other parts—*compensatory hyperæmia.* But all parts do not suffer equally, as they would do were the hyperæmia the result simply of increased arterial pressure; certain vessels, as the great abdominal veins, dilate, showing that the vaso-motor system arranges for the accommodation of the surplus blood by producing local diminution of vascular resistance. After extirpation of one kidney, its share of blood passes mainly to the other.

3. *By excitation of vaso-dilatator nerves*, such as the chorda tympani. Nothing is certainly known of this as a cause of hyperæmia; but the hyperæmia associated with facial neuralgia and that of the thyroid in exophthalmic goitre, have been referred to vaso-dilatator neuroses, and also to inhibition of vaso-tonic nerves.

Results.—The results of active hyperæmia are principally such as might be expected from increase, in any particular organ or tissue, in the amount of arterial blood and in the rapidity of its flow. The symptoms in a superficial part are—increased redness and pulsation, a subjective sensation of throbbing, some increase in bulk, and marked elevation of surface temperature, until this approaches that of internal organs. If the hyperæmia be of long duration, or frequently repeated, the small arteries remain permanently enlarged, their walls gradually thicken, and the epithelium and connective tissues of the part increase. This may be seen in the growth of hair and epidermis thickening round a callous ulcer of the leg, and the occasional spread of ossification from the tibia into the granulation-tissue, though *irritation* may possibly be an additional factor. The capacity for work is increased, and hypertrophy will follow if the increased work is maintained (p. 86). Hyperæmia of the nervous centres causes great excitability, paræsthesia of sight and hearing, and even convulsions. In some glands, hyperæmia

produced experimentally is followed by increased secretion, as in damage to the renal plexus, which is followed by the increased secretion of watery and even albuminous urine.

PASSIVE OR VENOUS HYPERÆMIA.

In passive or venous hyperæmia, the excess of blood is in the veins and capillaries, and the flow, instead of being accelerated, is retarded. This is so frequently produced by some obvious mechanical obstacle to the return of blood through the veins, that it is often called *mechanical* hyperæmia. The congestion of a finger, produced by a moderately tight band tied round it, may be taken as the type of passive hyperæmia.

Causes.—Anything which weakens the forces carrying on the venous circulation, or which opposes unusual resistance to this circulation, must tend to produce venous hyperæmia. Such causes may exist in any part of the vascular system—heart, arteries, capillaries, or veins—some having a local, others a general effect. They may be arranged under two headings—(1) those which *diminish* the *vis a tergo*, or propelling force; and (2) those which *introduce* a *vis a fronte*, thus placing a direct impediment to the return of blood by the veins.

1. Chief in the first group is **diminished cardiac power.** The heart may act so feebly or be so damaged structurally (see Endocarditis), that too little blood enters the arteries at each stroke, and generally at a pressure less than normal. As a result the arterial supply of all parts is diminished, blood lags in the veins, and a less quantity than normal returns to the heart during each diastole. This is very evident in prolonged febrile diseases, such as typhoid, and in those degenerations of the walls of the heart which lead to dilatation of its cavities. In whichever of these ways the *vis a tergo* is impaired, the diminished fulness of the arteries and over-fulness of the veins, so familiar clinically as the result of *cardiac failure*, will be produced. If this condition be of long duration, there is necessarily so much interference with the oxygenation of the blood, with the functions of the blood-forming organs, and with the processes of digestion and assimilation, that the blood itself becomes deteriorated, and thus the nutrition of all suffers.

In the arteries the driving force may be weakened (1) by total or partial *obstruction* of an arterial trunk; (2) by *dilatation*, arising from simple atony, or from those general fatty, atheromatous, or fibroid changes of the arterial wall so common in advanced life may perhaps lead to some local diminution in the blood-pressure. (3) It is often said that in cases of *rigidity*, or loss of arterial elasticity, the heart's force is wasted against the walls of rigid tubes. It is not clear that any serious obstruction to the blood-stream will be produced, unless there is simultaneous narrowing of the lumen of the vessel: this is frequently the case in atheromatous arteries.

Obstruction to the circulation **in capillaries** arises mainly from pressure of inflammatory and serous effusions on capillary areas.

With regard to veins, the circulation will be slowed by: (1) absence

or diminution of contractions on the part of the skeletal muscles, especially in the lower extremity; (2) such dilatation as produces incompetence of valves, thus rendering muscular action useless as an aid to circulation; and (3) by anything which lessens the suction-action exerted upon the great veins by the respiratory movements of the thorax. Forcible expiration will replace the normal *minus*-pressure within the thorax by a *plus*-pressure: thus, playing wind-instruments impedes the entry of blood from the veins into the heart. Emphysema, effusion of air or fluid into the pleural cavities, and large new-growths of the lung act similarly. These causes might fairly rank under the second heading.

When, by various combinations of the above conditions, the circulation is much retarded, **hypostatic congestion** occurs. The commonest seats of this are the posterior edges and bases of the lungs, the skin over the sacrum, and any parts kept constantly dependent. Slowing of the circulation causes distention of the veins and increase of the intravenous pressure. In any such part which is also dependent, the intravenous and capillary pressure is further increased by *gravity*. The force of gravity is in proportion to the vertical distance between the highest point of the body for the time being and the part in question. If the patient is so weak as to be unable to change his position, this pressure constantly acts upon the same veins and capillaries, dilating them, and greatly increasing the tendency to leakage through their badly nourished walls. Thus the part is redder and softer than normal, and is œdematous (p. 206). In bedridden patients breathing is often very shallow, and the effect of expiration in driving blood on to the left auricle is therefore diminished (see Hypostatic Pneumonia). In people who are walking about, dropsy from heart-disease generally begins in the legs. This is due largely to the action of gravity.

2. The return of blood through the veins may be interfered with in many ways. Thus, congestion of the stomach, intestines, pancreas and spleen, from compression of the portal capillaries, occurs in cirrhosis of the liver; congestion of the lung follows mitral constriction or regurgitation; congestion of the systemic circulation results from insufficiency of the tricuspid valve; and in the lower extremities the same result may be due to pressure of the gravid uterus on the iliac veins.

In addition to the above causes, the *sudden removal of pressure* may produce hyperæmia. Thus, congestion of the abdominal vessels follows the removal of much ascitic fluid, or of a large ovarian tumor; bleeding from the pleura occurs when the cavity is rapidly emptied by aspiration or strong syphon-action; bleeding may also follow the complete emptying of a chronically distended bladder. The walls of such vessels, being thus provided with external support, gradually lose their power; if, then, the support is suddenly removed, the vessels dilate fully, and small ones may even rupture.

Results.—Whether there be a direct impediment to the return of blood by the veins, or a failure in the forces of circulation, the veins **and capillaries dilate**, and the blood, moving with diminished velocity, **accumulates in them.** The subsequent changes will depend upon the

degree of obstruction to the venous return, and upon the arterial pressure; in other words, upon the injury sustained by the vessel-walls from impaired nutrition, and upon the increase of pressure in the veins and capillaries. In addition to the immediate effects, such as the diminished secretion of urine, the more gradually induced changes are the exudation of serum, the escape of red blood-corpuscles, hemorrhage, fibroid induration, atrophy, thrombosis, and necrosis.

1. **Exudation of serum** is one of the most important results of passive hyperæmia. It is discussed on p. 204).

2. **Escape of red blood-corpuscles** occurs when obstruction to the venous return is very great: they transude with the fluid from the veins and capillaries. The blood-stream in these vessels stagnates, and the red corpuscles become packed into a coherent mass which oscillates to and fro with the arterial pulsation. Then, suddenly, some of the red corpuscles penetrate the walls of the capillaries and smallest veins and escape into the surrounding tissues. This seems to occur without rupture of the vessel, for, if the ligature be removed, the blood again circulates in a perfectly normal manner. The corpuscles rarely escape in great numbers. It has been suggested that they pass by diapedesis between the endothelial cells.

3. **Hemorrhage** is another result of passive hyperæmia, and usually occurs only when the obstruction to the venous current is very great, and when the nutrition of vessels and tissues has suffered from long congestion. Healthy vessels can bear very heavy strains without giving way. Those vessels which are the least supported are the first to give way. Hemorrhage into the stomach in cirrhosis of the liver, and into the lung in mitral stenosis, are familiar examples of this result.

4. **Fibroid induration** is due to a gradual increase in the connective tissue round the bloodvessels, and is one of the most important results of long-continued passive hyperæmia. This interstitial growth was formerly supposed to lead to atrophy of the higher structures, and thus to impairment of the functions of the organ. In the stomach, it was said to produce atrophy of the glandular structures; in the kidney, compression of the tubules; and, in the heart, diminution in motor power. It is probable, however, that the **atrophy** in these cases is primary, following the deficient supply of arterial blood, and that the increase in the stroma is due to the fact that the latter is the only tissue present that can thrive in the existing conditions. We must also take into consideration the possible stimulating effects of irritant products or of dead epithelial cells on the growth of the fibrous tissue; but the importance of this factor is difficult to estimate. The alterations which this change produces in the physical characters of the organ—viz., induration associated with abnormal redness, due to the excess of blood or pigmentation from hæmatoidin—are exceedingly characteristic.

5. **Thrombosis** (see p. 208).

6. **Necrosis** occurs from passive hyperæmia only when the obstruction is very general and complete (p. 32).

To sum up, long-continued passive hyperæmia leads to impairment of vitality and function. The tissues gradually undergo retrogressive

changes and atrophy, although from the amount of exudation and blood which they contain their size and absolute weight may be increased. This form of hyperæmia has no tendency to cause multiplication of tissue other than the *connective*, and, in the case of the skin and mucous membranes, the *epithelial*. In the latter instance the proliferation is associated with catarrhal inflammation, to which the congestion predisposes.

Morbid Anatomy of Hyperæmia.—Parts which were actively hyperæmic during life frequently show no signs of this condition after death; for, if coagulation does not occur immediately, contraction of the arteries or of the elastic capsules of organs forces the blood on into the veins, thus rendering the recognition of arterial or capillary hyperæmia impossible. Further, under the influence of gravity alone, fluid blood will tend to run to the more dependent parts: and thus a hyperæmic organ—whether actively or passively congested—may be emptied of blood and may thus appear pale.

But, on the other hand, dependent parts—the posterior portions of the lungs, the lowest coils of the intestines, the skin on the posterior surface in dorsal decubitis—which may have been healthy during life, now become full of dark blood. It is often difficult to say how much of the congestion of the base of a lung is ante-mortem and how much post-mortem.

When large veins are hyperæmic, the injection is said to be "ramiform," from their branching form and dark-blue color. In the intestine, skin, and kidney, hyperæmia may appear punctiform from the arrangement of the vessels in villi, papillæ, or Malpighian corpuscles, as the case may be. Minute punctiform hemorrhages must not be mistaken for such cases.

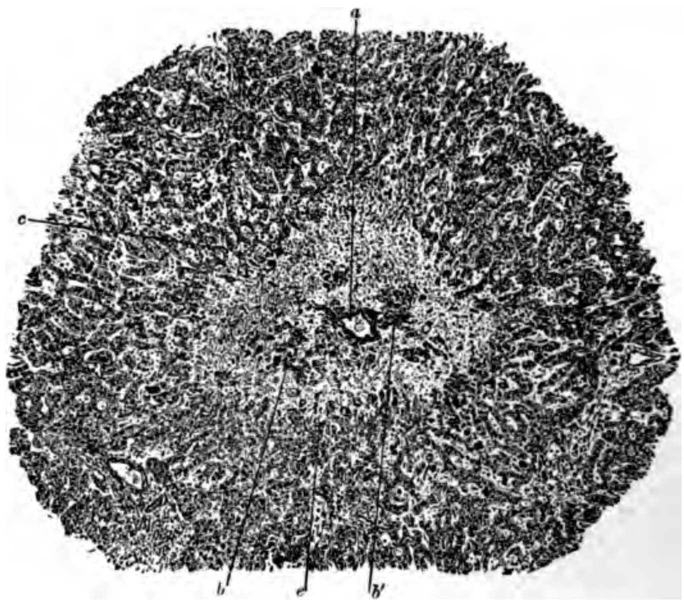
Pigmentation (slate-gray, black or brown) from the altered hæmoglobin of disintegrated corpuscles (p. 81) generally remains after chronic hyperæmia, as is often seen in the stomach and intestines after portal congestion, and in the bladder and the lungs after chronic catarrh.

Passive Hyperæmia of the Liver.

Passive hyperæmia of the liver is the result of some obstruction to the blood-stream in its course from the hepatic veins until it reaches the aorta. It may thus be due to the pressure of inflammatory tissue or exudation on the inferior vena cava; to fibrosis or emphysema of the lung; and especially to disease of the mitral or the tricuspid orifice associated with failing compensation on the part of the walls of the heart. Long-continued passive hyperæmia of the liver gives rise to the condition known as *nutmeg liver* (Fig. 108). The change is characterized by a large accumulation of blood in the sublobular and intralobular veins, which dilate and thicken; by distention of the supplying capillaries and venules; by atrophy of the hepatic cells in the central portions of the lobules (*cyanotic atrophy*); and rarely by increase of the interlobular connective tissue. The impediment to the return of blood by the hepatic veins leads to atrophy of the cells in the

central portions of the acini and to the deposit of pigment, so that, when examined microscopically, these portions of the acini are seen to consist of masses of broken-down cells and granules of pigment,

FIG. 108.



Passive hyperæmia of the liver. A single lobule. *a*, distended intralobular vein with thickened walls; *b*, *b'*, isolated groups of degenerated liver-cells surrounded by enormously distended capillaries and atrophied liver-cells; *c*, fatty liver-cells. × 100.

separated from one another by the distended vessels. The intralobular veins and their radicles are much dilated, and filled with red blood-corpuscles (Fig. 109). Their walls are thickened, and there often

FIG. 109.

Passive hyperæmia of the liver. Two capillaries near central hepatic vein. Showing the thickening of the walls and the accumulation of red blood-corpuscles within them. × 500.

appears to be some thickening of the intercellular network which immediately surrounds the central vein. Owing to this thickening of

the central vein and of the adjacent intercellular network, and to the destruction of the liver-cells, the most central portions of the acini, in advanced stages of the disease, may appear to show a greater increase of fibrous tissue than has actually occurred. At the peripheral parts of the acini new fibrous tissue is occasionally seen between the almost unaltered liver-cells. In a few instances this may be a prominent feature.

In the earlier stages of this affection the liver is smooth and often considerably increased in size from the large amount of blood which it contains. On section, it presents a peculiar mottled appearance, the centre of the lobules being of a dark-red color, whilst the peripheral portions are of a yellowish-white. This latter appearance is occasionally increased by fatty accumulation in the peripheral liver-cells. The appearance of such a section is not unlike that of a nutmeg (Fig. 110).

FIG. 110.

Passive hyperæmia of the liver. a, a^1, a^2, intralobular veins, round which the liver-cells have atrophied. This zone appears pale, as the red corpuscles, with which the distended capillaries are crowded, are unstained. The external zone is fatty, but stains in the usual manner. To the naked eye, in unstained sections, the central zone is dark, and the peripheral fatty zone pale. × 25.

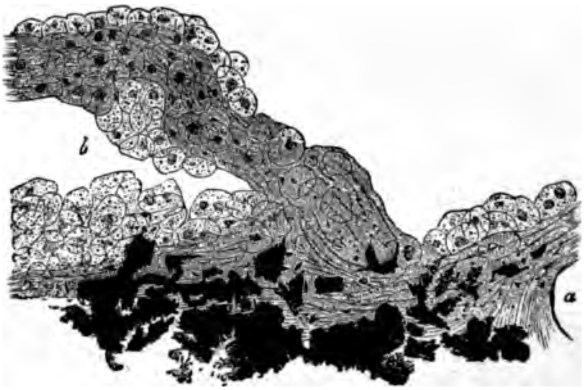
Ultimately, the organ may undergo a gradual diminution in size, becoming more or less irregular on the surface. This is due to atrophy of the central cells of the lobules, mainly from malnutrition (p. 195), but partly from pressure of the dilated central veins and the contracting interlobular growth.

Passive Hyperæmia of the Lungs.

In the lungs, long-continued passive hyperæmia produces that peculiar induration and pigmentation which is known as **brown induration.** This most frequently results from stenosis of the mitral orifice or from insufficiency of its valves. The consequent changes consist, in the first place, of elongation and dilatation of the pulmonary capillaries,

so that even in uninjected preparations the alveolar walls appear abnormally tortuous. The epithelial cells lining the alveoli become swollen, probably multiply, and are seen in large numbers, filled with dark-brown pigment, covering the alveolar walls (Fig. 111). They fre-

FIG. 111.



Brown induration of the lung. Showing the abnormal number of swollen pigmented epithelial cells covering the alveolar walls, the increase of connective tissue around the bloodvessels, *a*, and the large quantity of pigment; *b*, the alveolar cavity. × 200.

quently accumulate within the alveolar cavities. These changes are followed by an increase in the interlobular connective tissue, by the formation of large quantities of brownish-black pigment, and often by a thickening of the alveolar walls. The bronchial mucous membrane is dark and the small peribronchial vessels are dilated. Sometimes these vessels rupture and blood is extravasated into the tissue of the lung. Not infrequently these changes occur with and after infarction (p. 222), a closely associated condition.

Lungs in which these changes are at all advanced present a more or less uniform brownish-red tint, mottled with brown or blackish-colored specks and streaks. They are heavier, tougher, and denser, as well as less crepitant than normal.

DROPSY.

The normal tissues are continuously bathed in, and nourished by, the lymph, which derives its nutritive material from the blood, and passes on into that fluid the products it receives in exchange from the tissues. These products find their way, either by the veins or by the lymphatics, back to the heart, and thence to the lungs, skin and kidneys. In all probability the veins are quite as much the soil-pipes of the tissues as the lymphatics. To state that there is, in all parts of the body, a constant circulation of lymph, transuding from the capillaries and returning by the lymphatics, is more than is justified by our present knowledge. In the dog, at any rate, we know that during rest there is no flow at all from the lymphatics of the limbs. The

lymphatics seem to perform most of their work during active exercise, or in any local emergency.

Lymph varies both in amount and in composition. The two factors which are mainly operative in determining these are—(1) the excess of the pressure within the capillaries over that in the tissues immediately around them; and (2) the special properties of the cells of the capillary walls.

1. The **capillary pressure** is, in general terms, a sort of resultant between the arterial and venous pressure. It usually follows most closely that in the veins. If either the arterial or the venous pressure rise or fall, while the corresponding venous or arterial pressure remains *constant*, the capillary pressure will rise or fall too, as the case may be. If, however, one of them, either the arterial or the venous pressure, rise or fall while the other moves in a *contrary* direction, the resulting capillary pressure may rise, remain constant, or fall. Under such circumstances the capillary pressure is difficult to estimate, for there is no method of direct measurement. Most often, as has been said, it follows that in the veins. A statement regarding the arterial pressure alone is rarely a safe guide to the capillary pressure, partly for the reason just given, and partly because the arterioles may interpose an additional indeterminate factor.

2. The influence exercised by the **capillary walls** upon the production of lymph has been supposed by Heidenhain and others to be of the nature of an active secretory process, but by many it is still regarded as a passive factor, the efficacy of which depends only on the efficient nutrition of the vessel-walls. According to this second view, a vessel-wall is said to be more or less "permeable" in proportion to (1) the readiness with which it allows fluid to transude (sensitiveness to pressure); and (2) the resemblance which the transuded fluid bears to the plasma of the blood. Thus, so long as the pressure remains constant, the *permeability of the capillaries* determines both the amount and the composition of the lymph. For example, the capillaries of the liver are said to be more permeable than those of the intestine, and those of the intestine than those of the limbs. By this is meant that a similar increase of pressure induced in each case will not be followed by a similar result, but that there will be a marked increase of the lymph-flow from the liver, a less increase from the intestines, and the smallest increase of all from the limbs; and that in any case the lymph from the liver will contain more proteid matter than that from the intestines, and that from the intestines more than that from the limbs. The saline constituents are the same in all cases, and correspond in amount to that found in the blood-plasma. It is well known that ascitic fluid contains more albumin than œdematous fluid from the legs, and that this is so under all conditions, and does not depend on the disease producing the dropsy. *Damage*—such as dipping a limb into very hot water—increases the permeability of the capillaries, and, therefore, both the amount of fluid transuded and the resemblance which it bears to blood-plasma. It is probable that a

somewhat similar but less pronounced change may be caused by gradual alterations in nutrition, due to the circulation of defective or vitiated blood, and that increased friction and greater permeability may result.

Heidenhain found that by introducing certain substances into the blood he could produce an increase in the flow of lymph. These substances he called "lymphagogues," believing that they in some way stimulated the supposed secretory power of the capillary walls. Starling has, however, shown that, in the case of dextrose, the first effect of its introduction is to cause a reabsorption of fluid into the bloodvessels, and a consequent increase in the total quantity of fluid they contain. This in its turn produces a rise in the venous, and therefore in the capillary, pressure; and to this increased pressure rather than to any special secretory process he attributes the additional lymph-flow. Starling further shows that if an amount of blood equal to the expected absorption—caused by the introduction of the dextrose—be previously withdrawn, no increase in the total amount of blood, no rise of the venous pressure, and no addition to the ordinary lymph-flow, will occur. It seems, therefore, that *permeability* should still be regarded as depending on a diminished power of retention rather than as an active secretory process.

By *dropsy* is meant the retention of lymph, either in connective-tissue spaces or in serous cavities, though by some writers it is used only with reference to the latter. The term *œdema* is limited to dropsy of the connective-tissue spaces, while *anasarca* means œdema of the subcutaneous tissue. Thus we speak of "general dropsy," "œdema of the lungs," "anasarca of the legs."

It is practically certain that the causes of increased lymph-flow are also the causes of dropsy. It is quite certain that the most marked examples of dropsy are, in practice, associated with **marked increase in venous pressure** acting over a long period. Among these, *local obstruction* to the return of venous blood plays the chief part. This may be caused by the pressure of cicatricial tissue, or of a tumor, or by thrombosis. *Inefficient action of the heart*, such as that occurring in late stages of valvular disease, causes a fall in arterial, but a rise in venous, pressure, with a consequent slowing of the circulation. As the veins become distended their valves become incompetent, and the action of gravity on the enlarged blood-column adds enormously to the pressure in the capillaries of the legs and thus produces anasarca. A slighter form of œdema of the legs, in women whose occupation involves much standing, is due to the combined influence of constipation, garters, and gravity. In all these cases the passive congestion probably increases the *permeability* of the capillary walls. The certainty that the increased venous pressure is the cause of the dropsy rests mainly on the constancy with which the dropsy disappears when the increase in pressure is removed. *Increased arterial pressure* is sometimes credited with the production of dropsy, but it is uncertain whether, in the absence of increased venous pressure, it is a sufficient cause. No convincing proofs of such a mode of causation have been given. In that form of chronic Bright's disease known as "granular kidney" there is a marked

increase in the arterial pressure, but it is generally stated that no œdema occurs until the heart's action begins to fail, and the venous pressure consequently rises. Possibly in such conditions the contracted arterioles may partially neutralize the effect and act as a guard to the capillaries. As a matter of fact, many cases occur in which œdema is associated with chronic renal disease without any other signs of cardiac failure; and it seems that the above statement is too absolute. In such instances the œdema is, however, more probably due to toxic substances present in the blood (*see* below) than to the increase of arterial tension. An experiment of Heidenhain's shows how fallacious it is to trust to arterial pressure as a guide to capillary pressure. By obstructing the thoracic aorta, this observer enormously reduced the arterial pressure. Notwithstanding this reduction, he found that the combined lymph-flow from the intestines and liver together showed no proportional fall, though the lymph obtained included an appreciably larger amount of proteids. Heidenhain's inference was that no process of mere tissue-filtration could possibly explain the result. Starling repeated this experiment, but took the precaution of measuring the pressures in the portal vein and in the inferior vena cava, as well as in the femoral artery. He found that the enormous fall in the arterial pressure was accompanied by a considerable drop in that in the portal vein, but by a distinct rise in that in the inferior vena cava; so that, although the pressure in the intestinal capillaries was almost nil, the pressure in those of the liver was probably increased. He further showed that the flow of lymph from the intestines ceased, while that from the liver (normally the more concentrated) continued, as might have been inferred from the pressure conditions. In this way the changes in capillary pressure were found to explain the alterations in both the quantity and character of the lymph.

The second great division of dropsy comprises those cases associated with **inflammation of the kidneys** and deficient urinary secretion. In renal dropsy the exuded fluid contains a smaller percentage of proteid and a larger percentage of extractives than in dropsy due to increased venous pressure, although the same proportionate difference between the composition of the ascitic and subcutaneous fluid obtains. The urine in renal dropsy generally contains a large amount of albumin, and the consequent diminution in the albumin of the blood possibly affords some explanation of the small amount in the dropsical fluid. Moreover, in these cases there is no ascertained increase of venous pressure. It is true that the pressure in the arteries is often raised, but the rise bears no uniform relation to the œdema. Possibly the dropsy is due to the action of some toxic substances upon the capillary-walls, whereby their permeability is increased. There is, however, no constant relationship between dropsy and uræmia, which is also believed to depend on a similar cause. It has been suggested that in these cases there are substances circulating in the blood which act like the experimentally injected dextrose, and that these substances produce a condition of *plethoric hydræmia* and a consequent general rise of blood-pressure followed by œdema. Recent experiments tend to show that

in chronic renal disease there is deficient excretion of sodium chloride, which consequently tends to accumulate in the tissues. The œdema of Bright's disease may be consequent upon this accumulation, causing withdrawal of fluid from the blood into the spaces of the connective tissue.

In cardiac failure there must be some hindrance to the exit of lymph from the thoracic duct, and this may be an adjunct in dropsy due to cardiac causes. Local pressure on the lymphatics does not usually produce œdema, though the occasional presence of chyle in the urine, or in the pleural or peritoneal cavities, is generally attributed to blocking of the respective lymphatics by growths or parasites, or to rupture of the thoracic duct or receptaculum chyli.

In anæmia, neuralgia, exophthalmic goître, tumors of the spinal cord, and other diseases, slight degrees of œdema are occasionally met with. Section of the spinal cord produces vaso-constrictor paralysis, and tumors probably act in a similar manner. In the other cases vaso-motor derangements are common, and though their cause is less definitely ascertained, paralysis of vaso-constrictor, or direct action of vaso-dilatator nerves is probable, and would furnish a sufficient cause. Experimental anæmia gives rise to no increased lymph-flow, but it does not follow that defective blood acting over a long period might not increase the permeability of the capillaries. Experiments on the spinal cord, and on the splanchnic and vagus nerves, have hitherto failed to afford satisfactory evidence of the existence of any nervous cause of œdema apart from vaso-motor changes.

Localized areas of œdema of the skin are met with in the condition known as *urticaria*. This disease is often associated with the presence of toxic matter in the blood, derived as a rule from the alimentary canal. In some instances a similar condition is apparently produced by the action of the nervous system, slight stimulation of the skin (pressure) being followed by the appearance of urticarial wheals (*urticaria factitia*).

THROMBOSIS.

Thrombosis is the *coagulation* of the blood within the vessels during life. The product is called a **thrombus**, in opposition to a **coagulum** or **clot**—the result of post-mortem coagulation. Thrombosis may occur in the heart, arteries, capillaries, and *especially in the veins*. It is by no means certain that the process of coagulation is the same in all cases.

Causation.—Thrombosis is generally said to be due to one or more of *three* causes: damage or absence of the lining cells of the vessel-walls; retardation of the blood-stream; and changes in the blood itself increasing its coagulability.

I. Damage or Absence of the Lining of the Vessel-wall.—When coagulation of circulating blood occurs, it is usually upon some obviously diseased surface. It is probable that the influence of the vessel-wall is neutral or passive so long as it is living and healthy. Thus the normal vessel-wall may be compared to greasy and viscous substances, like vaseline, paraffin and castor oil, in contact with which blood may be kept filled for long periods, and yet be ready to coagulate normally as soon as it touches rough solid matter to which the corpuscles can adhere.

Although the *vessel-wall* has been spoken of, the **integrity of the en-**

dothelial layer is alone necessary. Fatty and calcareous changes of the deeper structures do not cause thrombosis, whilst atheromatous ulcers, foreign bodies, and nodules of new-growths—all uncovered by endothelium—may; moreover, severe injury of capillaries, which possess only endothelium, causes thrombosis in them. *Damage or absence of the endothelium* of the bloodvessels is the most important condition in the production of thrombosis. This damage or absence, as already stated, may be due to many causes.

1. *Injuries may destroy or injure the endothelium.* Among the most important of these are section, rupture, ligature, and torsion of vessels. In section and rupture, thrombosis starts from the damaged intima and constitutes part of the process by which hemorrhage is naturally and temporarily arrested (p. 217). Cauteries and caustics furnish other examples of the effect of injury in producing thrombosis.

2. *Diseases of the vessel-walls may affect the endothelium.* Thus, thrombosis may occur on atheromatous ulcers, on bare calcareous plates, or on an intima damaged by syphilitic inflammation, or by the extension of spreading inflammations from other parts.

There is some uncertainty concerning the part played by *the walls of the veins* in the production of thrombosis. The influence of inflammation of the walls (*acute phlebitis*) in *pyæmia* is considered elsewhere (*see* Diseases of Bloodvessels, Chapter XI.); but venous thrombosis is also a frequent complication in many chronic wasting diseases, specific fevers, and other disorders. Pyogenic or other micro-organisms are present in most of the thrombi occurring in these cases, and in some of the instances there is but little doubt that an infective phlebitis has preceded the thrombosis (Welch). The organisms may be derived from the blood circulating in the affected veins. As in endocarditis, they cause necrosis of the endothelium, thus giving rise to fibrin-ferment, while, later on, they lead to inflammatory changes in the vessel-wall. It is possible that in some cases the organisms may reach the vessels by way of the vasa vasorum or lymphatics.

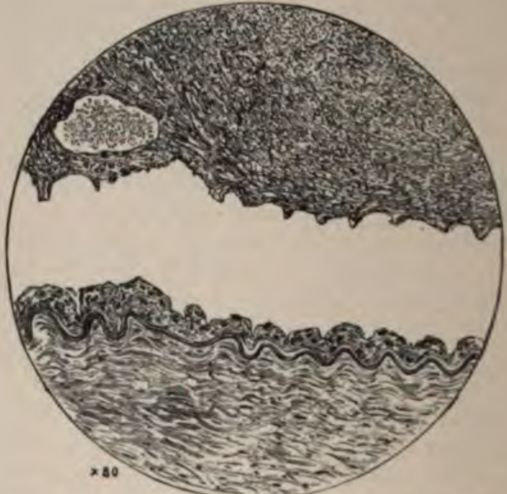
3. *Imperfect blood-supply to a part, causing disease of the vessel-walls by imperfect nutrition.* Here slowing of the circulation is the indirect, and deficient vascular supply the immediate, cause. It is probably not a very important group, as there are reasons for supposing that the nutrition of the intima may be maintained by the circulation in the vasa vasorum, apart from that in the affected vessel (Fig. 112; see Inflammation of Arteries), and there is no necessary relationship between these two portions of the circulation. This cause is chiefly operative in the case of the smallest vessels. The conditions affecting the blood-supply will be considered in a subsequent section.

4. *The presence of foreign bodies in the vascular system.* These comprise such things as needles, horsehair, or wire introduced into the sac of an aneurism; pre-existing clots (thrombi or emboli); parasites, such as Distomata, which have penetrated the vessels; and new-growths which project into the interior of veins. In all these instances the thrombus forms first upon the foreign substance itself. The roughness of the surface of the foreign body seems to be a factor of some im-

portance. Zahn introduced small glass balls without producing any thrombosis.

II. Retardation of the Blood-stream.—Sometimes the causes just considered (abnormality of surface) are insufficient to cause extensive clotting, until retardation of the blood-stream is added. For example, in the *aorta* we sometimes find calcareous plates uncovered by endothelium, but with little or no adherent fibrin. In *aneurisms*, too, the wall is always abnormal and the circulation somewhat retarded; but sufficient

FIG. 112.



Section of a thrombosed popliteal artery, a fortnight after ligature, showing persistence of almost the whole of the intima. The thrombus has been torn from the vessel-wall. × 80. (Mott.)

clotting to effect a cure may not occur until, by treatment, we still further reduce the current, and thus prolong the contact of the blood with the abnormal surface. In *veins*, however, where the blood-current is slow, slight lesions in the walls are rapidly followed by thrombosis.

On the other hand, retardation, or even arrest, seems unable by itself to produce thrombosis. So long as the endothelium is kept fairly nourished and the blood is of normal quality and free from micro-organisms, the stagnant blood does not coagulate.

How are these different results to be explained? Impaired circulation in a part means damage to all the tissues supplied—to the endothelium of the vessels among others. It is, of course, possible that diminishing the rapidity of the blood-stream may have no other influence than that which it exerts in this direction. There are, however, reasons for assigning to it a more direct action. All parts of a stream flowing through a tube do not proceed at the same rate. The central or axial part of the stream invariably travels faster than the peripheral or periaxial, for it is exposed to less friction. If solid particles be suspended in such a fluid, those with a specific gravity most closely approach-

ing that of the fluid will move most rapidly, and maintain their position in the axial stream most easily. If the rate of flow be diminished, the tendency of the suspended particles to remain in the axial stream will also diminish, and this will be in proportion to the difference between their respective specific gravities and that of the fluid in which they are suspended.

In most arteries and in many veins the periaxial stream contains only plasma and a few leucocytes. But directly the stream slackens leucocytes leave the axial stream in large numbers and lag behind close to the walls, while even the red corpuscles maintain less perfectly their axial position. The blood-platelets generally occupy the axial stream, but fall out soon after the leucocytes, and from the same cause. Now whether we attribute to the leucocytes or to the platelets the chief function in the production of the thrombus (p. 212), it is quite evident that, though the lining membrane of the vessel be diseased, yet the increased friction thereby produced may be insufficient to cause any practical slowing of the blood-stream at that point, and insufficient, therefore, to bring either platelets or leucocytes into contact with the damaged part of the wall. In this way we may have an abnormal endothelial lining without any resulting thrombosis.

FIG. 113.

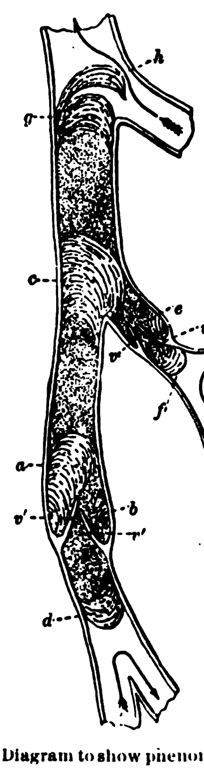


Diagram to show phenomena of venous thrombosis. *v*, *v'*, valves of veins; *a*, *b*, primary thrombus (white); *c*, *d*, *e*, *f*, *g*, secondary white thrombi connected with primary white thrombus by various red thrombi; *h*, piece of white thrombus becoming detached by blood current. (Modified from Thoma.)

On the other hand, when the current is slow, as in the veins, the leucocytes and platelets will readily come into contact with the sides of the vessel and may produce clotting, even though the damage to the vessel-wall be comparatively slight. In this way we find that neither damage to the endothelium nor slowing of the circulation need be followed by thrombosis; and that the former is the more important cause of the two, because there are many places where the blood-stream is naturally slow. The occurrence of local eddies in the blood-stream is probably of considerable importance in determining the occurrence and position of thrombi (Fig. 113).

A tendency to stagnation of blood may be due to many causes, of which the most important are cardiac weakness, general diminution of vascular tonus, and dilatation (*varix*) of veins. All these are often present in a single case and, combined with the action of micro-organisms, are the principal factors in the causation of the "marasmic clots" of Virchow. These form *in the most dependent veins* —*e.g.*, those of the lower limb, pelvis, or back; *in the cerebral veins*

and sinuses, where the venous circulation is ordinarily very slow and difficult; and *in those parts of the heart* in which blood tends to remain when the organ first fails to contract efficiently—*e. g.*, the auricular appendices, the apices of the ventricles, and the spaces between the trabeculæ. In veins these clots begin just behind the flaps of valves (Fig. 113). The force of the venous current is so slight, or the resistance to it so great, that it no longer opens the valves completely; the blood consequently stagnates, and, after a time, coagulates behind the cusps. Such clots occur in the course of many exhausting diseases—as phthisis and cancer—in which thrombosis is materially facilitated by the quiescent state of the patient.

In varicose veins, which are frequently the seats of thrombosis, the circulation is extremely slow, and the endothelium, owing to imperfect nutrition, can scarcely ever be healthy, though it is not always so damaged as to excite coagulation.

III. Certain conditions of the blood seem to favor coagulation and to promote the occurrence of thrombosis. It is said that the tendency to coagulation is increased during the later months of pregnancy, after profuse hemorrhage, and in certain acute inflammatory diseases, such as acute rheumatism, erysipelas, pneumonia and pleurisy. The only two ascertained changes in the blood, likely to lead to thrombosis, are (1) the presence of micro-organisms, and their products, and (2) an increase in the platelets. The *micro-organisms* may, in addition to their other results, assist thrombosis by producing "clumping" of the red corpuscles. The *platelets* may be found in large numbers at the end of many of the acute fevers, constituting a "platelet-crisis" (Hayem), while a moderate increase has been often observed in anæmia, spleno-medullary leucocythæmia and other diseases. To whatever cause it may be due, an increased tendency of the blood to coagulate is probably never more than a predisposing cause of thrombosis.

It is well known that the presence of calcium salts is essential to the coagulation of the blood; while the addition of oxalates will neutralize the effect of their presence and prevent coagulation. So also, among the products of cell-action, substances allied to nuclein aid coagulation, while albumoses hinder it. The bearing of these facts upon the phenomena of thrombosis is at present unknown.

Characters of Clots and Thrombi.—Post-mortem coagula in the *heart* are generally *buffy*. The thickness and firmness of the pale layer generally varies with the time which elapses before the changes in the heart-substance allow coagulation to begin, but is to some extent dependent on the tendency of the red corpuscles in certain diseases—*e. g.*, pneumonia—to form dense clumps instead of more open meshes or rouleaux: its position indicates the part that was uppermost after death. Though not adherent, the clots are often so much entangled among the chordæ and trabeculæ, that they cannot readily be removed. Post-mortem clots in the *vessels* are *red*, *soft*, and never adherent.

They do not *fill* the vessels, and can be easily drawn out of them as long strings.

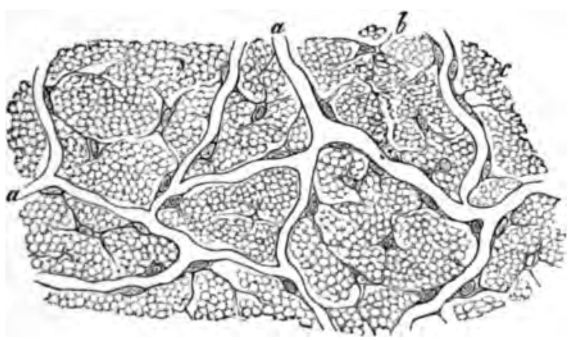
Thrombi or **ante-mortem clots** are of two kinds—**red** and **white**, according as they originate from *stagnant* or from *circulating* blood.

In the former case, as seen in an artery or vein after ligature, more or less of the stagnant blood on either side of the knot coagulates into an ordinary **red** clot—soft, uniform on section, and adherent to the vessel-wall where this is injured. The thrombus, still adhering to the wall, then contracts, becomes drier and less elastic, but still remains red. This is the state in which a red thrombus is generally found. If the surface of a *red* thrombus be exposed to circulating blood, a layer of *white* thrombus may be deposited on it (Fig. 113).

When coagulation occurs in blood *which is still circulating*, as in the sac of an aneurism or on a cardiac vegetation, a **white** or **mixed** thrombus results.

This is made up of a mass of blood-platelets, fibrin and leucocytes. According to Welch, the first deposit in a white thrombus consists of

FIG. 114.



Section of an arterial thrombus—thirty-seven days old. *a*, new bloodvessels; *b*, leucocytes and anastomosing cells. (Rindfleisch.)

platelets in the form of pale roundish bodies, in size averaging a quarter of that of a red corpuscle. In a short time, between and at the edges of the masses of platelets, a deposit of uninjured multinucleated leucocytes begins, and shortly afterward fibrin appears at the same places. Ordinary *white thrombi* are grayish-white or reddish in color, firmly adherent to the vessel-wall, and usually stratified. Examined microscopically, they are found to consist of granular masses made up of altered platelets and separated from one another by fibrin, leucocytes, and a larger or smaller number of red corpuscles (Fig. 114).

A thrombus may be either *parietal* (forming one or more laminæ attached to the vessel-wall) or *obstructive* (completely filling up the lumen), thus causing either partial or complete occlusion of the vessel. A *parietal* thrombus is always of the white variety, while an *obstructive* thrombus may be either *red* or *white*. Once formed, both varieties extend in the same way, by the formation of a red thrombus where the blood is

stagnant, and by the deposition of platelets, fibrin and leucocytes where it is circulating. A parietal may be thus converted into an obstructive thrombus. The extension of the latter is generally checked by the rapidity of the blood-current at the junction of the first large collateral branch in each direction (Fig. 113); but sometimes, especially in veins, the thrombosis continues, and a clot may extend from the veins of the foot to the vena cava. Both in arteries and veins, extension is most likely to take place in the direction of the circulation, though it may occur in an opposite direction. Obstructive thrombi generally adhere to the wall throughout their whole length, but sometimes they do so only at their points of origin.

A few rare forms of thrombus are occasionally met with. (1) *Hyaline thrombi.* In the smallest vessels, and especially in the capillaries, there are sometimes found refractive homogeneous translucent plugs, readily colored dark blue with Weigert's fibrin-stain. These are probably derived either from platelets or directly from red corpuscles. (2) *Fibrinous thrombi.* Masses of fibrin are occasionally found blocking the smaller vessels, especially in the consolidated portions of the lung in acute pneumonia. (3) *Leucocytic thrombi.* Vessels are sometimes found filled with leucocytes, but it is doubtful if these should be regarded as true thrombi.

Final Changes in Thrombi.—Thrombi may remain with but little change beyond *decolorization*, or they may undergo *softening* or become *organized*.

Decolorization.—The first change in a red thrombus is a breaking-down of the red corpuscles. Their stromata become unrecognizable, and the hæmoglobin is set free and in great part absorbed, though some may remain as granular hæmatoidin. As a result, the thrombus loses its deep red color and acquires a finely mottled reddish-gray tint. The process begins in the centre, and takes weeks or months before it is completed.

Long thrombi, such as occur after ligature of the lower part of the carotid, as well as large laminated thrombi, like those in aneurisms, may remain for long periods as more or less granular masses of non-irritant fibrin, without any sign of organization or of softening.

Calcification may occur in these thrombi as a late change, and thus give rise to *phleboliths*. These are especially common in the prostatic plexus.

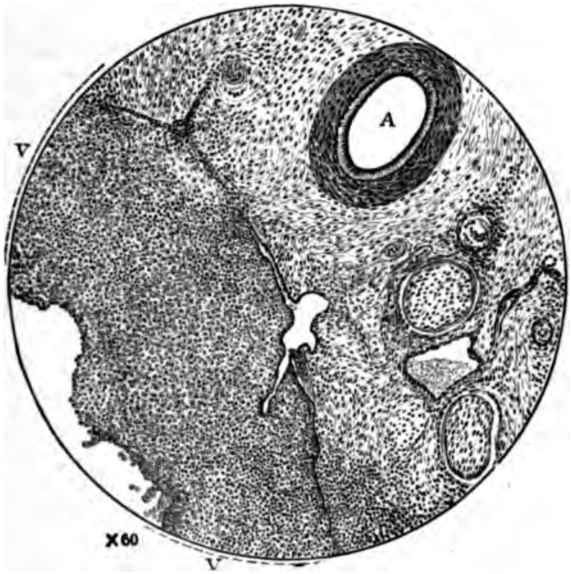
Softening.—That thrombi can disappear and leave the lumen of the vessel pervious is certain; for when it was the custom for venesection to be performed at regular intervals, the repeated bleedings were frequently effected from the same vein. In modern times also, re-establishment of the circulation is known to have occurred through spermatic veins and through the superficial veins in the leg, in cases where thrombosis had undoubtedly taken place.

The process by which this occurs is not known, but in a large number of cases it is probably the result of some form of softening process. Soft-

ening may be *simple* or *infective*. Infective softening is invariably due to pyogenic or putrefactive organisms. Organisms are often found in simple softening, but this variety is not infective, and probably has some other cause.

1. *Simple softening*.—The changes commence by the disintegration of the centre of the thrombus and by the formation of a more or less

FIG. 115.



Section through a portal canal in a case of suppurative pylephlebitis arising in connection with "umbilical pyæmia." The vein-wall (V) is converted into granulation-tissue. Lumen of vein is below on the left. × 60. (Boyd.)

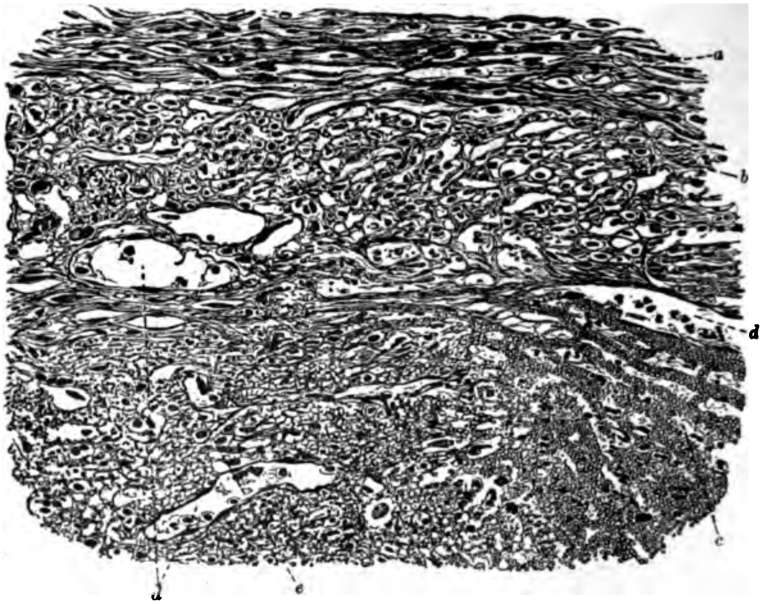
fluid, pappy substance, which has a reddish-gray color, varying with that of the thrombus which is undergoing the change. To the naked eye the fluid often looks like pus, and the process is still sometimes spoken of as the "puriform" softening of a clot. But Virchow long ago pointed out that the fluid consisted of the débris of corpuscles and fibrin—albuminous, fatty, and pigmentary granules. There may be a few recognizable white corpuscles in it, which have probably migrated from without. In cases of constriction of the mitral orifice of the heart, with consequent dilatation of the left auricle and slowing of the circulation, large clots undergoing this change may be found in the auricles. They consist of little more than bags of thick, grumous fluid. The outer laminæ generally form a firm case for the softened central part, and if the softening approach the surface, this case is often thickened at that point by the formation of fresh protective clot. Not infrequently, however, the encasing clot may be perforated and the contents discharged into the circulation. The larger particles may form emboli (p. 219), probably too minute to cause symptoms. When the contents of an

obstructive thrombus occurring in an artery or vein are thus discharged, the circulation in the vessel may be re-established through the centre of the thrombus. This process constitutes one form of *canalization* of a thrombus.

2. *Infective softening.*—Certain cases of *puriform* softening, similar, so far as the naked eye can detect, to the above, are accompanied by all the symptoms of septic poisoning. The wall of the affected vein is found acutely inflamed and often suppurating (Fig. 115); while any portions of the clot which enter the circulation are so charged with organisms that suppuration ensues wherever they are lodged (see Pyæmia). The *Streptococcus pyogenes* is the organism most frequently present, and to it the infective properties of the broken-down clot are due. In the great majority of these cases the veins affected lead directly from a wound, and then the mode of entry of the specific micrococci is evident. In many cases, no direct infection can be traced. When infective softening is due to putrefactive bacteria the thrombus is converted into a stinking yellowish red fluid.

Organization.—Organization of thrombi is most frequently observed

FIG. 116.

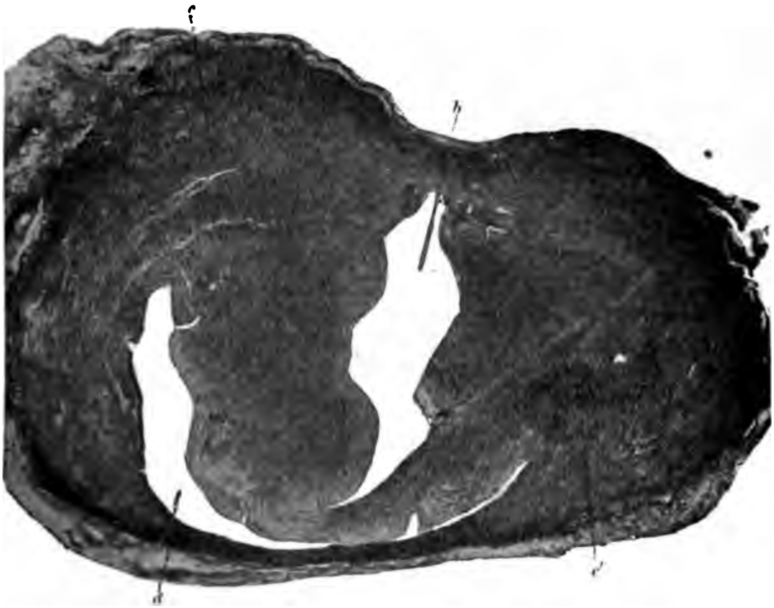


Organization of a thrombus. *a*, middle coat of vein; *b*, proliferation of cells of internal coat; *c*, portion of unaltered thrombus infiltrated with leucocytes; *d*, spaces lined by spindle-cells forming the new vessels in the organized thrombus; *e*, site of old thrombus now occupied by spindle-cells and fibrillated tissue. × 200. (From a specimen by J. D. Rolleston.)

in arteries which have been ligatured. By this procedure the middle and internal coats are divided; the cut ends of these at once retract and become inverted, while a red thrombus forms on each side of the liga-

ture, extending from the divided ends until it almost or quite reaches the first collateral branch. The thrombus thus formed undergoes the changes described under decolorization, and gradually disintegrates, playing a purely passive part in the subsequent process. The cut ends of the vessels undergo proliferative inflammatory changes. The intima becomes thickened, and the internal elastic lamina obscured and in places

FIG. 117.

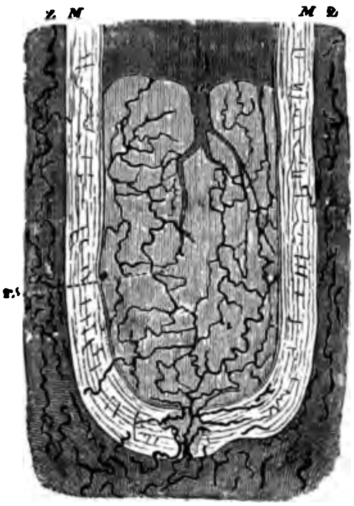


Organized thrombus. The thrombus is replaced by a mass of fibrous tissue lined with endothelium. Two large channels have been formed, one (a) between the wall of the vein and the thrombus; the other (b) through the thrombus (canalization). Where the organization is most complete (c, c') the wall of the vein is thickest. × 15. (From a specimen by Dr. Rolleston.)

broken up. The clot becomes gradually invaded and replaced by new cells derived from the endothelium and fixed connective-tissue cells of the vessel (Fig. 116) by what is apparently a proliferative inflammation. Channels lined with these cells traverse the clot, and here and there separate it from the vessel-wall (Fig. 117). These ultimately form bloodvessels connected with the now enlarged vasa vasorum, by means of vessels entering by the cut end or by the spaces where the internal elastic lamina has disappeared. The vessels (Fig. 118) and channels (Fig. 117) in the clot occasionally communicate with the blood in the ligatured vessel; eventually the clot becomes entirely replaced by fibrous tissue, reducing the affected portion of the vessel to a mere cord. In venous thrombosis the vessels and channels in the thrombus may communicate with the lumen of the vessel on both sides. In this way, by another form of *canalization* (p. 216), the circulation may become more or less completely re-established. This is especially

frequent at the junction of the common iliac veins in cases of *white leg* (*phlegmasia dolens*). It is rare in arteries. Complete organization depends to a large extent upon the nutrition of the affected vessels, the maintenance of asepsis, and the general health of the patient.

FIG. 118.



Longitudinal section of the ligatured end of the crural artery of a dog—fifty days after the application of the ligature. Showing the newly formed vessels in the thrombus and their communication with the vasa vasorum. *Th*, thrombus; *M*, muscular coat; *Z*, external coat and vasa vasorum. × 20. (O. Weber.)

Results.—The results of thrombosis comprise certain changes in the walls of the vessels, more or less obstruction to the circulation, and embolism. These must be considered separately.

1. Changes in the Vessels.—Changes in the wall of the vessel are an invariable consequence of the formation of a thrombus. The changes which occur in the *organization of a thrombus* are really changes in the vessel-wall (p. 217); and when the thrombus undergoes a process of *infective softening*, acute inflammation takes place in the vessel-wall (p. 216). In many cases, however, the inflammation precedes as well as follows the thrombosis, and must be regarded as its immediate cause.

2. Obstruction to the Circulation.—The consequences of the obstruction to the circulation, resulting from the formation of a thrombus, will depend upon the rapidity and manner of its formation, the nature and size of the vessel obstructed, the situation and number of the collateral branches and the force of the circulating current. The rapidity with which the obstruction is effected is of considerable importance, inasmuch as the more gradual the process the longer is the time allowed for the establishment of a collateral circulation. For this reason the interference with the circulation caused by thrombosis is, for the most part, less marked than that which results from the more sudden obstruction caused by embolism.

The obstruction to the circulation may lead, in the case of an artery, to (1) *necrosis* of the tissues supplied by it (p. 35), with or without *infarction* (p. 223), and in the case of a vein, to (2) *dropsy* (p. 204). Necrosis is especially likely to result from obstruction in the *cerebral vessels*, as the nutrition of highly specialized tissues, like the brain, suffers directly their blood-supply is interfered with. Infarction is a more frequent sequence of embolism than of thrombosis, and will be considered in the next section.

In the *veins*, when thrombosis occurs in a vessel of small size and when collateral branches are numerous, as in the prostatic or uterine plexuses, the circulation is but little interfered with, and no symptoms of obstruction result. If, however, the main trunk of a large vein, as

the ilio-femoral, becomes obliterated, the obstruction is followed by passive hyperæmia and dropsy, the extent and duration of which will depend upon the facility with which the circulation can be restored by the collateral vessels. It must be remembered, however, that the valves in veins when they exist may, by preventing back-flow, offer a great impediment to collateral circulation. Thrombosis in the ilio-femoral vein frequently occurs, as already stated, in the later stages of many chronic debilitating diseases, especially in phthisis and in enteric fever; also in the puerperal state, where it is frequently found in *phlegmasia dolens*. The extent of the *thrombus*, the number of collateral branches which it blocks, and the strength of the circulation, will do much to account for the amount of œdema.

The results of obstruction in arteries are considered elsewhere (p. 222).

3. **Embolism.**—Portions of the thrombus may be carried away by the circulation, thus constituting embolism. This, which is the most important result of thrombosis, will be considered in the following section.

EMBOLISM.

Embolism is the impaction of solid substances, circulating in the blood, in vessels which are too small to allow them to pass. A mass thus arrested is termed an *embolus*.[1]

The most frequent sources of emboli are (1) *venous thrombi*, portions of which are carried by the blood-stream from the seat of their formation. The other sources are: (2) fragments, especially of thrombi, detached from the walls or inflamed valves of the heart (see Endocarditis), or less frequently from the inner surface of arteries; (3) portions of new-growths—as sarcomata—which, having perforated the vessels, have been carried away by the current; (4) parasites which have made their way into the interior of vessels; and (5) pigment-granules. (6) Fluid fat which has escaped from the fat-cells and entered open lymphatics—an occasional occurrence in fractures and contusions—may perhaps produce embolism, but the possibility of this occurrence is doubtful.

A **thrombus** may produce emboli in various ways. (1) It may soften and break down, and its fragments be distributed by the blood-current. (2) Portions of a parietal thrombus, not filling the vessel, may be detached by the passing stream. (3) *The most frequent way* is that illustrated by the accompanying diagram. A thrombus usually ceases at the junction of the vessel containing it with the first large collateral branch. The end of the thrombus—in arteries as well as in veins—nearest to the heart often extends as a firm conical projection into the lumen of this collateral branch (Fig. 119); and the strength of the blood-current, which is the chief factor in preventing the further extension of the clot toward the heart, may break off this projecting end and sweep it into the general circulation. Some sudden movement or exertion often determines, in these cases, the separation of the fragment which is to form the embolus. Thrombi in the veins of the lower extremities,

[1] ἔμβολος, a plug.

in the uterine veins, and in the jugular veins are the most frequent sources of this accident.

Emboli become arrested in the first vessels which are too small to allow them to pass. Usually, therefore, the seat of impaction will be at the bifurcation of a vessel, or at some point where, from the giving off of large branches, the calibre diminishes suddenly (Fig. 120). The particles may be so small as to pass through even the finest capillaries, and not give rise to any symptoms; or they may pass through large capillaries, like the pulmonary, to be arrested in a finer set beyond; but, as a rule, they are impacted either in the first set of capillaries to which they come, or in some larger vessel between these and their seat of origin. Thus emboli originating in the systemic veins, in the right cardiac cavities or in the pulmonary artery, will most commonly become arrested in the vessels of the lungs. Emboli originating in the pulmonary veins, in the left cardiac cavities, or in the arteries, will be similarly impacted in the systemic arteries and capillaries, especially in those of the spleen, where the circulation is slow; and of the brain and kidney, where the capillaries are very small. Finally, emboli originating in any of the organs supplying the portal venous system will block branches of the portal vein in the liver. With the exception, therefore, of emboli originating in the portal system, the seat of arrest is usually the arteries or capillaries.

FIG. 119.

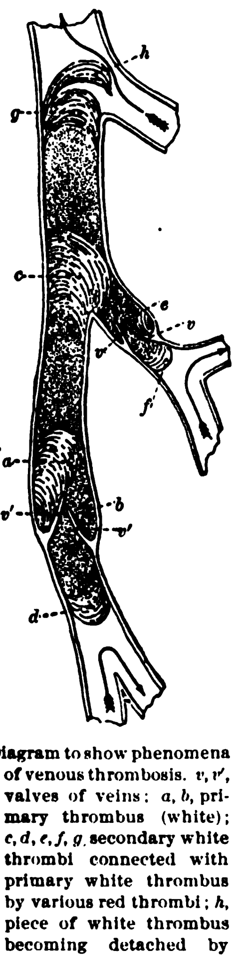


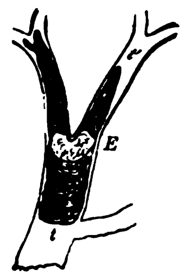
Diagram to show phenomena of venous thrombosis. v, v', valves of veins: a, b, primary thrombus (white); c, d, e, f, g, secondary white thrombi connected with primary white thrombus by various red thrombi; h, piece of white thrombus becoming detached by blood current. (Modified from Thoma.)

Emboli are carried usually in the direction of the main current; hence those carried by the aortic stream pass into the thoracic aorta more commonly than into the carotid or subclavian vessels, and into the left carotid or left renal artery more often than into the corresponding artery of the opposite side. Gravitation also influences the direction in which they are carried, especially those of large size, which move somewhat more slowly than the blood-stream; hence, they are more common in the lower lobes and posterior parts of the lungs than in the superior and anterior portions of these organs (p. 227). It is found experimentally that small bodies injected at intervals into the jugular vein are often swept into the same division of the pulmonary artery.

It is not uncommon to find that the small vessels of an area, of which the supplying artery is plugged, also contain emboli. This may be accounted for in two ways. *First*, if, as is frequently the case, the

arrest takes place at a point of bifurcation, the embolus may not be large enough to block either branch, but may allow a small stream of blood to pass into each vessel; this may break off portions of the original embolus, and so produce secondary emboli, which become impacted in the smaller divisions of the same main trunks. The *second* mode is by the detachment of several small fragments from some distant source, which subsequently yields a mass large enough to block the main trunk.

FIG. 120.



Embolus impacted at the bifurcation of a branch of the pulmonary artery. Showing the formation of thrombi behind and in front of it, and the extension of these as far as the entrance of the next collateral vessels. E, embolus; t, t', secondary thrombi. (Virchow.)

The amount of obstruction which immediately follows the arrest will depend upon the *nature* of the embolus as well as upon its size and shape. If the embolus be from a soft, recently formed thrombus, it will be at once moulded to the cavity of the vessel, which will thus be immediately and completely plugged. If, on the other hand, it is irregular in shape and firm in consistence, as when derived from a calcified cardiac vegetation, it may not completely fill the vessel, but allow a small current of blood to pass.

The arrest of the embolus, and the consequent obstruction to the circulation, is followed by the formation of *thrombi* (secondary), behind and in front of it, which extend as far as the junction of the first large collateral vessels (Fig. 120). If the embolus does not completely fill the vessel, successive layers of thrombus are deposited upon its surface until the occlusion of the vessel is complete, and then the secondary thrombus extends, as in the former case, until it meets with a current of blood strong enough to arrest its progress. If the embolus is a portion of a red thrombus, it will in most cases be impossible to distinguish it from the secondary thrombus which surrounds it. If, however, it is a calcareous mass, or a portion of a white thrombus, it may usually be distinguished from the more recent secondary coagulum.

Fragments of a damaged liver have, in rare cases, been carried from the right auricle through a patent foramen ovale, and thus lodged in the kidney or the brain without passing through the lungs. To this phenomenon the name of *paradoxical* or *crossed embolism* has been applied. In other equally rare instances, portions of venous thrombi or of new-growths projecting into the interior of the veins seem to have made their way up-stream towards the capillaries. This procedure is possibly due to some intermittent and local reflux of blood. The condition is known as *retrograde embolism.*

Emboli, derived from thrombi, may undergo the same secondary changes as the latter (p. 214).

Effects.—The results of embolism may be divided into (1) those depending upon obstruction to the circulation, and (2) those due to the composition of the emboli.

I. Effects due to Obstruction to the Circulation.—Sudden and complete arterial obstruction may produce (1) no noticeable effects beyond certain changes in the vessels, such as are necessary for the restoration of the circulation under the altered conditions; (2) slight damage to the tissue-elements, in some cases only noticeable from the consequent functional defects; or (3) necrosis of the whole area supplied by the obstructed vessel. These effects again depend upon (1) the extent of the arterial anastomoses, (2) the readiness with which these can be utilized, and (3) the dependence of the affected part on its blood-supply.

(1) *Extent of Arterial Anastomoses.*—When the arterial anastomoses are free and the vessels concerned are healthy, the sudden and complete obstruction of an artery, such as the radial, is followed by contraction of the central end of the obstructed artery—from the site of the block to the nearest collateral branch—and by dilatation of the arteries in the area supplied by the blocked vessel, as well as of those through which blood can be conveyed to them. The dilatation of the latter vessels follows, and possibly depends upon, increased velocity of the blood-stream (Thoma); and both changes are probably due to the lowered resistance in the anastomosing vessels, and not to increased pressure from behind, as is shown by the contraction of the upper part of the obstructed vessel already alluded to, and by the limitation of the increased blood-flow to those arteries which actually supply the anastomosing vessels.

Infarction.—In some organs, such as the spleen and kidney, the arteries have capillary, but no arterial, anastomoses with the neighbor-

FIG. 121.

White infarct of the kidney. The whole of the pale area is necrosed, and the darker central part is undergoing secondary changes. The dark area outside is due to hyperæmia.

ing vessels. Such arteries are called *end* or *terminal* arteries. Each of these arteries supplies a conical compartment of the organ in question. The base of the cone is on the surface of the organ, while its apex points toward the centre, and corresponds to the point of entrance and exit of the artery and vein respectively. The possible means of access which the blood has to such a portion of tissue are, the main artery and vein just mentioned, the small vessels passing from the capsule into the cortical part of the organ, and the capillary anastomoses with the neighboring vessels on each side.

If the main artery supplying one of these conical segments of tissue

becomes blocked, necrosis and degenerative changes will occur in it; for the capsular vessels and the lateral anastomoses together are unable to maintain the nutrition of the part. If the tissue thus deprived of blood be freely supplied with coagulable lymph it will undergo coagulation-necrosis and form a pale, solid, clearly defined cone, known as a **white infarct** (Fig. 121). In some organs and under some circumstances the necrosed area will gradually become infiltrated with red corpuscles, and a blackish-red cone with a slightly raised base will be formed. This is known as a **red infarct** (Fig. 123). Recent infarcts of both kinds are surrounded by a hyperæmic zone (Fig. 121). *Red infarcts* are common in the lungs and intestine and *white infarcts* in the kidney and retina. Infarcts in the spleen and in the muscular walls of the heart may be white or red. When no coagulable lymph is present, as in the brain, necrosis occurs without infarction.

Later Changes in Infarction.—In the case of a small red infarct, *if the embolus is free from virulent organisms*, the coagulated blood gradually loses color, becoming brown or yellow, and absorption proceeds slowly. In the case of a similar small white infarct, the tissue-changes are more clearly seen than in the red infarct, where they are obscured by the extravasated blood. In the white infarct, lymph reaches the part by transudation from parts around, the cells swell, lose their nuclei, and blend—in fact, undergo coagulation-necrosis (p. 36): thus the well-known white wedges are formed. The more external portions of this mass of coagulated blood and necrosed tissue become infiltrated with multinucleated leucocytes, and a pink layer of granulation-tissue is gradually formed around the mass. The granulation-tissue is subsequently replaced by fibrous tissue: this contracts, and ultimately a depressed scar may be all that remains to indicate the change. The central parts of a large infarct may soften, but the general changes and ultimate results are the same.

If pyogenic cocci are present in considerable numbers suppuration will follow, and the infarct become converted into an abscess (see Pyæmia).

(2) *The effects of arterial obstruction will also depend upon the readiness with which the existing anastomoses can be utilized.* Bier maintains that there is a marked physiological difference between the limbs and the viscera in this respect—the existing anastomoses being readily available in the limbs, but not in the viscera. In some instances, however, the inefficiency of existing anastomoses is capable of a mechanical explanation. Spasm of the intestine interferes with the circulation in its walls (Mall), and spasm of the intestine is one of the earliest results of embolism of the superior mesenteric artery. The spasm is, therefore, a sufficient reason for the failure of the anastomoses to preserve the nutrition of the intestine, which generally undergoes gangrene when a branch, supplying more than two inches of its length, is blocked.

Calcification or other disease of the anastomosing vessels, or of the arteries supplying them, by preventing dilatation may interfere with the restoration of the circulation in the affected part, and thus lead to gangrene.

(3) *The organs in the body vary much in the extent to which they depend upon the regularity of their blood-supply.* Among those which are most susceptible to defects in the circulation are the cells of the central nervous system, intestine and kidney. Obstruction of a common carotid artery may be followed by partial hemiplegia and, if it is maintained, by cerebral necrosis, although no other artery supplying the circle of Willis is blocked. The ganglion-cells of both brain and spinal cord die if deprived for half an hour of their blood-supply. Temporary blocking of the renal artery in a rabbit for two hours is followed by necrosis of many of the epithelial cells (Litten). The tissues of the skin and periosteum are probably the least susceptible of all.

Cessation of function soon follows cessation of nutrition. The effects of this may be extremely serious; thus, plugging of one of the larger cerebral arteries is generally followed by sudden loss of consciousness and paralysis; plugging of the pulmonary artery, by sudden asphyxia; and plugging of one of the coronary arteries, by sudden paralysis of the heart.

Pathology of Red Infarction.—Very different explanations have been offered of the exact source of the blood in a red infarct.

Cohnheim thought that when emboli blocked terminal arteries, hemorrhagic infarction was the almost invariable result. In his opinion, and according to his results, blocking of the artery was at once followed by regurgitation of blood from the principal veins into the capillaries, which thus became engorged. Red corpuscles then made their way through the capillary walls into the surrounding tissues, the permeability of the capillaries having been increased by deprivation of arterial blood. This view at the present time finds but few supporters. Other observers, repeating Cohnheim's experiments, failed to see the regurgitation which he described; while it has been conclusively shown (1) that, if both artery and vein are simultaneously blocked, the subsequent hemorrhage will be still more marked; and (2) that if, in addition to the main artery, every other source of blood-supply except that through the principal vein be closed, necrosis without any hemorrhage will result; or, in other words, that red infarction will not occur. Nor does increase in the permeability of the vessel-walls appear to be an important factor, for though, as Cohnheim pointed out, deprivation of the blood-supply for many hours will cause increased permeability of the capillary walls, yet hemorrhagic infarction can take place long before any such change in the vessel-wall has been produced.

In all probability the diapedesis of the red corpuscles depends on marked slowing of the arterial current, by which all distinction between the axial and peri-axial streams (p. 210) is lost, combined with marked increase in the capillary and venous pressure. The red corpuscles are thus brought into contact with the capillary walls, and possibly pass, along with the lymph, between the endothelial cells (Welch). The natural permeability of the capillaries, which is known to be different in different parts of the body, may not improbably be a factor in the process.

Litten showed that red infarction of the kidney usually depends on the integrity of the capsular arteries, and that it does not occur if these are separated from the kidney before the main artery is blocked. The results of Mall and Welch, however, furnish the most convincing proofs. These observers ligatured all the vascular communications of the intestine, with the exception of the main artery and vein, and then tied the bowel above and below so that the included portion was supplied by the main artery, and the blood returned by the main vein. Under these circumstances no infarction resulted. They then gradually constricted the main artery, and found that when it was sufficiently compressed to stop the lateral pulsations in its branches, or, in other words, to reduce the pressure in them to about one-fifth of the normal, hemorrhagic infarction appeared. The same observers in other experiments found that the same reduction of arterial pressure generally occurred when infarction was in progress. Why some infarctions are red, and others white, seems therefore to depend, as has been suggested, on local differences in the blood-pressure. If the arterial pressure does not fall below seventy-five per cent. no infarction occurs, if it falls from between seventy-five to eighty per cent. red infarction results, and if it falls to zero, white infarction follows. Daniel finds that red infarcts are usually associated with infective embolism, white infarcts with impaction of aseptic material.

These observations will also explain why, in the large majority of cases, no infarction occurs when a truly terminal artery is blocked; and why an infarct in the spleen may follow thrombosis in the splenic veins without any obstruction in the artery.

II. Effects due to Composition of the Embolus.—A *simple embolus*, such as a piece of non-infective fibrin or a fragment of a calcareous plate, with its secondary thrombi, will usually be absorbed or lead to proliferative arteritis and organization (p. 216). An *infective embolus*, that is, one containing micro-organisms and derived from an infective source, may in some instances only produce results similar to those caused by a non-infective embolus. Infective emboli of somewhat greater virulence may lead to a more acute form of arteritis in which the intima and internal elastic lamina are destroyed and the media weakened—an aneurism not infrequently resulting. This is indeed now held to be the pathology of most aneurisms occurring in people too young to be suffering from atheroma or acquired syphilis; and, as the emboli are usually small or of moderate size, aneurisms from embolism affect especially the cerebral arteries and the smaller arteries of the limbs, from the size of the brachial downward.

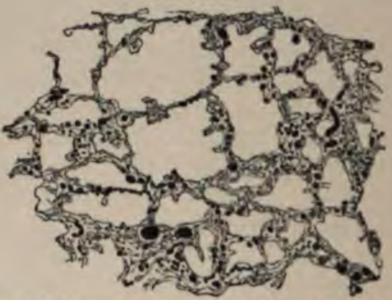
Virulently infective emboli give rise in most cases to suppuration in addition to the other results of embolism already described (see Pyæmia).

Capillary Emboli.

It has been stated that fat, masses of organisms, clumps of white blood-corpuscles, pigment-granules, and bubbles of air, may all give rise to embolism of capillary vessels.

Fat Embolism.—In fractures, contusions of subcutaneous tissue, ruptures of fatty liver, acute osteomyelitis, and other morbid conditions in which fat-cells are broken up and the fat set free, the droplets are

FIG. 122.



Fat-embolism of lung. From bad compound fracture of leg and severe subcutaneous laceration. The black masses are drops of fat, stained with osmic acid, lying in capillaries and arterioles of alveolar walls. × 40. (Boyd.)

absorbed by the lymphatics and veins, especially when pressure in the part is increased by inflammatory effusion or hemorrhage. On reaching the right side of the heart they are carried into the pulmonary arterioles and capillaries, where their presence may easily be demonstrated by staining with osmic acid (Fig. 122). One by one these soft and easily moulded plugs are swept on to the left side of the heart, and distributed by the systemic circulation to other organs, in which also they may be very numerous. For a time fresh globules are constantly reaching the lungs, but when this ceases the fat-masses are passed on to other organs and eliminated, in part at least, through the kidneys. Fat-embolism is believed by some to be the cause of death after simple fractures—a very rare event. But as large quantities of fat may be introduced into the vessels of the lungs of animals without causing any symptoms whatever, some scepticism is justifiable. If a sufficiently large number of the capillaries of the lung, or any other organ, be blocked by fat, its function will, of course, be interfered with; and in the case of some organs this would mean speedy death. It is probable that the lungs always contain, proportionately, many more emboli than any organ supplied by the systemic circulation. It has been ascertained that half the pulmonary blood-path may be obstructed without the general circulation being thereby disturbed (Cohnheim). It is therefore supposed that, as a rule, the passage of fat on to the systemic circulation keeps the number of plugged capillaries below the point of danger. It must be borne in mind that fat is practically fluid at the temperature of the body, so that it is doubtful whether embolism can result except from displacement of whole groups of fat-cells. In acute osteomyelitis it is probable that the fat-drops may serve as carriers of pyogenic cocci from the seat of inflammation and cause the impaction of these organisms in vessels which they would otherwise pass through freely.

Air entering the veins has been stated to give rise to embolism; but

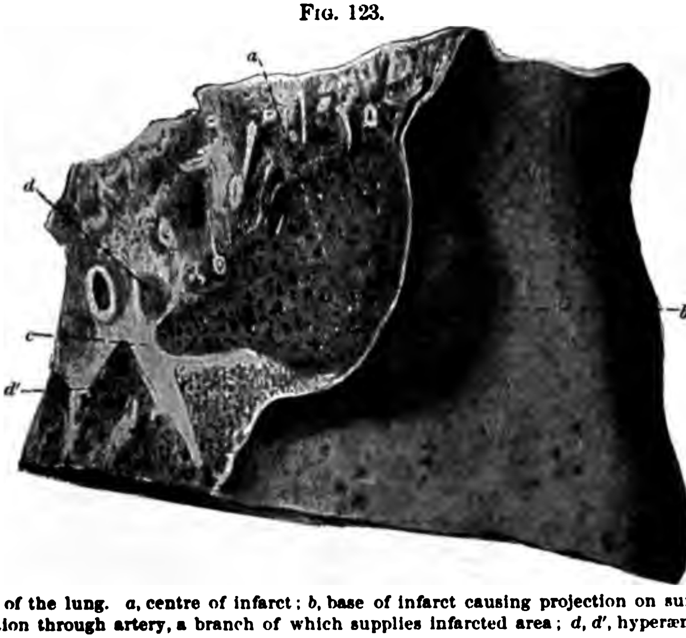
as air is not a solid substance, but is capable of passing through the vessels, it is doubtful whether such an occurrence is possible. The most probable explanation of death after the entrance of air into veins is that the right ventricle becomes filled with a mixture of air and blood, which is churned into a foam : this the heart is unable to force through the pulmonary vessels. Death is due to failure of the right side of the heart.

Clumps of leucocytes, and possibly of bacteria, may form emboli, giving rise to petechiæ, in septic fevers. *Pigment-granules*, probably parasitic in origin, have caused capillary embolism in malaria (p. 249).

Infarction of the Lung—Pulmonary Apoplexy.

The so-called infarcts of the lung are most commonly met with in cases of mitral stenosis, and to a less extent in those of mitral regurgitation. They are found in the lower lobes and in the lower and outer parts of the upper lobes. In most cases they are irregularly conical, but occasionally nearly globular (Fig. 123). In diameter they

FIG. 123.



Infarct of the lung. *a*, centre of infarct; *b*, base of infarct causing projection on surface; *c*, section through artery, a branch of which supplies infarcted area; *d*, *d'*, hyperæmic lung tissue.

vary from that of an entire lobe to a fraction of an inch. Blackish red, firm, dry, with well-defined margin, often multiple and occasionally confluent, they present superficial resemblances to tumors on the one hand and to lobar pneumonia on the other. From the former they are distinguished by their color, shape, position, and the conditions under which they occur; from the latter, by their number, shape,

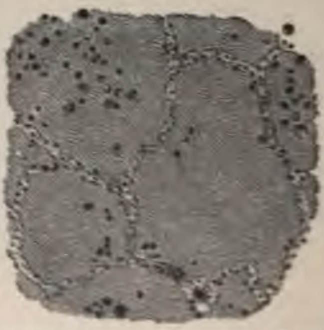
darker color, and better defined limits. They are not infrequently the starting-points of a hypostatic pneumonia, and are then less easily recognized. In such cases the adjacent portion of the visceral pleura is roughened by the inflammatory exudation on its surface, while, in the substance of the organ, the masses are welded together, their color mottled, and their edges obscured.

Mode of Formation.—There can be no doubt but that these masses consist of extravasated blood and of tissue which has undergone coagulation-necrosis; or, in other words, that they are red infarcts; but there is considerable difference of opinion concerning the reason of their appearance in the tissues. They are variously regarded as the products of **embolism, thrombosis,** or **rupture** of the pulmonary vessels.

In favor of **embolism** of one or more branches of the pulmonary artery may be urged (1) the frequent existence of a thrombus in the right auricle; (2) the occasional discovery of an embolus in the largest artery entering the infarct; (3) the general resemblance which these masses bear to infarcts of the spleen and kidney; and (4) the possibility of producing them experimentally. *Against* **embolism** as the sole cause are (1) the not infrequent absence in these cases of thrombosis and all other known causes of embolism either in the systemic veins or in the right auricle; and (2) the still more frequent failure to find an embolus in any branch of the pulmonary artery itself.

That **thrombosis** is at least an occasional cause of "pulmonary apoplexy" is inferred from (1) the existence, in a few of the cases, of atheroma in the pulmonary artery; (2) the presence of a thrombus (without any sign of embolism) in the main artery supplying the

Fig. 124.



Infarction of the lung. The alveoli are crammed with red corpuscles and contain a few large pigment-bearing cells, probably leucocytes. The alveolar capillaries are less distended than in pneumonia. (See Fig. 93.) × 120.

infarct; and (3) the extreme retardation of the blood-current at the time the "infarct" is formed. On the other hand, all these phenomena may exist without any infarction.

Unquestionably the most constant condition present in these cases is a marked diminution in the velocity of the circulation and a long-continued and marked increase in the pressure in the pulmonary veins

and capillaries, combined in most cases with blocking of the main artery supplying the infarct.

It will be readily understood from what has already been remarked (p. 224) that these conditions are exactly those likely to produce infarction ; it is therefore reasonable to suppose that both embolism and thrombosis may be factors in its causation, and that it may in some cases occur without the presence of either of these conditions.

Embolism of a large branch of the pulmonary artery causes rapid death from heart-failure and asphyxia : experimental embolism of a medium-sized or small branch generally produces no marked change, as the anastomoses are free and usually sufficient. In disease, however, the lungs have in most cases undergone the changes described under Passive Congestion (p. 212), and the heart's action is generally feeble. It is therefore natural to find that in disease, more often than in experiments, embolism and thrombosis give rise to infarction.

Infarction can be produced in the lung experimentally by many different procedures. Simple plugging of a small branch of the pulmonary artery is never a sufficient cause ; but Fujiami found that infarction occurred if a main artery was simultaneously blocked.

Cone-shaped hemorrhages into the lung-tissue may be due to the *rupture* of over-distended vessels. Obstruction of a small bronchial tube occurs and leads to collapse of the corresponding part of the lung. The external pressure on the walls of the vessels in the collapsed area is consequently diminished, and this condition leads to the over-distention of the vessels and occasionally to their rupture.

CHAPTER VIII.

FEVER.

By the term "fever" is meant an abnormal rise in the temperature of the body, together with other changes due to increased combustion of the tissues and abnormal exchange in material.

Temperature in Health.—It is usually stated that the mean daily temperature of the body is 98.4° F. This statement is only approximately correct, for the temperature varies (1) in different parts of the body, (2) with the time of day, and (3) according to the age of the patient. The variations due to these factors are greater in disease than in health. (1) The normal temperature of the *surface* of the body is always lower than that of the *internal parts*. Moreover, it is lower in proportion as we pass from the trunk toward the periphery, as well as more liable to variation from change in external conditions. In the *mouth* it is about 98.3° F.; in the *axilla*, 98.4° F. (36.9° C.); and in the *rectum*, 98.9° F. (37.2° C.). It is essential, therefore, if results are to be compared, that all observations be made in the same place. Accurate results are most readily obtained in the *rectum*. The *axilla* is less liable to variations in temperature than the *mouth*. In infants the temperature may be conveniently taken in the fold of the groin. (2) The time of the observation must always be stated, for the temperature rises during the day, reaching its maximum between five and eight o'clock in the evening, and falls during the night to its minimum between two and six o'clock in the morning. (3) The average temperature of an infant or young child is slightly *higher* than that of an adult: in the aged it may be slightly *below* the average in the adult. The full range between all these extremes is from 97° F. to 100° F., though the average range is rather less (97° F. to 99.2° F.).

The regulating (thermotactic) mechanism is less easily disturbed as age advances. The temperature of young children is easily raised or depressed: an attack of crying may cause a distinct rise. In old age, on the other hand, when the exchange of material is small, the temperature is more easily depressed than raised. For this reason a slight rise of temperature in the aged is of much graver significance than in the average adult, and in the former even acute forms of inflammation may be present without any accompanying rise of temperature. The effect of food is to excite metabolism in the large mass of gland tissue connected with the alimentary tract, and to cause a slight rise of temperature: the taking of food may, therefore, quicken a rise or retard a fall. The effect of ordinary exercise is to produce a rise: severe exercise, such as prolonged running, may cause a rise of one or

two degrees or even more. Mental exertion, unless accompanied by excitement and muscular activity, has little effect upon the temperature. The greater activity of the tissues and the combustion of the ingesta are the most obvious reasons for the higher temperature during the day. A similar daily variation is observed in the respiration and pulse, in the discharge of urea, and carbon dioxide, and in the intake of oxygen. The diurnal variation, however, occurs in persons confined to bed and deprived of food, so that the explanation may lie in the diminution of tissue-activities during sleep. In those people who are in active work during the night, and are asleep during the day, the normal course of the temperature is reversed.

Symptoms of Fever.—Since the introduction of the clinical thermometer the term "fever" has come to be almost synonymous with that of "rise of temperature." This latter condition is certainly the most easily ascertained, the most readily recorded, and, on the whole, the most reliable symptom of fever. The course of the temperature in all febrile attacks is divisible into three stages: (1) the *onset*, or period of rise; (2) the *acme*, fastigium, or stationary period, during which the temperature is more or less at its height; and (3) the *fall*, decline, or period of defervescence.

The **onset** may be *sudden*, the temperature rising three to seven degrees before the end of the second day; or it may be *gradual*, rising every evening, and falling slightly every morning, until the full height is reached, as in typhoid fever. The sudden onset is frequently accompanied by an intense sensation of cold and a violent attack of shivering, known as a *rigor*. The arterioles of the skin are contracted, and though the internal temperature is rising rapidly, the skin is cooler than normal, and the ordinary loss of heat from this source is diminished. In children in whom the controlling power of the nervous system is less developed than in later life, a *convulsion* often takes the place of the rigor. The gradual onset may be marked by slight chilliness, but very rarely by rigors.

The **fastigium**, or second stage, may be over in a few hours, or may last for weeks. The temperature may remain at a fairly constant level, or it may oscillate several degrees each day.

The **final stage** of fever, like the onset, may be sudden or gradual. When sudden, it is said to end by *crisis*. The drop is often accompanied by "critical" sweating, or diarrhœa; and even when the internal temperature is normal, the patient, guided by the sensations usual in sweating, may feel uncomfortably hot. Sometimes the fall is so rapid and so marked that the patient may be in danger of dying, and may even die, of collapse. When the fall is gradual it is said to end by *lysis*. This is analogous to the corresponding form of onset, as the temperature falls by a series of morning drops, broken by slight rises in the evening. The special types of fever characteristic of some diseases are in all probability dependent on peculiarities connected with the growth of special parasites (see Malaria). When fever ends in

death, the temperature generally rises just before this occurs, and may occasionally go on rising for a short time afterward.

The **extent** of the rise of temperature varies greatly. Above 107° F. the fever is called *hyperpyrexia*, and a temperature at or above this point, enduring for any length of time, is usually fraught with the greatest danger to life. In such cases prompt measures are necessary to prevent death.

So-called *paradoxical* temperatures even up to 128° F. have been recorded as occurring in hysterical individuals who are very liable to disturbances of body-temperature. The extraordinary rise in temperature is often quite local, and is out of proportion to the general symptoms. Such cases should be viewed with the gravest suspicion.

Types of Fever.—A febrile temperature almost always exhibits a tendency to rhythmic daily **variation** like the normal temperature—being higher in the evening than in the morning. Sometimes the opposite is the case, and the temperature is then said to be of the *inverted* type. When the daily variation does not amount to much more than two degrees, the fever is termed *continued*. When the variation is greater than this, the fever is *remittent;* of this type *hectic fever*, which accompanies chronic suppuration, is a good example. When the drop between two maximum points reaches or falls below normal —so that there is a fever-free period—the fever is said to be *intermittent;* of this variety malaria is the type. In many instances the course of the temperature is quite irregular.

Effects of Fever.—High temperature is generally accompanied by cloudy swelling of the tissues, and, if prolonged, by fatty degeneration; poisons circulating in the blood have very likely a share in producing this result (p. 45).

Apart from rigors and chilliness, which are usually associated with the onset, the earliest symptoms, as regards the **nervous system**, are headache, incapacity for self-application, general sluggishness of mind, loss of self-control, and hyperæsthesia of the special senses. Delirium is frequent—at first at night, and for short periods only, but later on more marked and even constant. Vague muscular pains are common in early stages; even in their absence, unwillingness for exertion is marked. The muscles waste rapidly and their movements become weak and tremulous. The nervous system has a large share in producing tremor and prostration, and is responsible for such a symptom as constant picking at the bedclothes (*carphology*): general convulsions, as already mentioned, may occur in children. In fever the frequency of the **heart-beats** is increased. This result can be obtained experimentally by the application of heat. Yet the rapidity of the pulse bears no reliable proportion to the height of the temperature. It is much greater in some diseases than in others; for example, in scarlatina than in typhoid. The heart, among other muscles, fails progressively in quality and power, and as it does so its beat becomes more fre-

quent and less effective. Here again the nervous system may be partly at fault, the inhibitory influence of the vagus being impaired, but direct damage to the cardiac muscle is probably the most important cause. Similarly, arterial tone is progressively lost. The result of the progressive failure of the heart-force and arterial tone is that the pulse, which in a healthy individual at the commencement of a long fever is quick, full, strong, and often inclined to hardness from high arterial tension, becomes, as the disease progresses, quicker, softer, and fuller, though no further rise of temperature has occurred. The softness and fulness of the pulse are due to loss of arterial tone while the heart-beat is still strong; the softness increases as the arterial tone yields, and actual *dicrotism* of the pulse may result. Later on, the size diminishes as the still more rapidly beating heart fails to fill the vessels. Ultimately the pulse is very small, soft, and frequent, or, as it is termed, *thready*. Increasing frequency of pulse with a steady or falling temperature is often regarded as *the* sign of a failing heart; though the "quality" of the first sound really affords an earlier indication of its occurrence.

Respiration is quickened. This change, like the increased frequency of the pulse, is possibly due in some measure to the effect of the rapidly heated blood—in this case, on the respiratory centre, as it can be induced experimentally by similar means. The oxygen absorbed and the carbon dioxide exhaled are increased during the initial rise in temperature, but both fall to their normal level if the fever is prolonged.

Digestion is impaired, for the secretions from the glands discharging into the alimentary tract are diminished. Appetite is lost (*anorexia*), and its place is taken by thirst. The tongue is dry and often furred. There is usually constipation, due probably to sluggishness of the intestinal muscle, to lack of secretion, and perhaps to absence of some of the normal stimuli to contraction. **Excretion,** as tested by the rapidity with which certain ingesta appear in the urine, is said to be slow in fever. Although the amount of fluid taken is larger than in health, the urine is small in quantity, has a high specific gravity, yields a copious precipitate of urates, and contains an excess of urea, uric acid, potassium salts, and pigment (*pathological urobilin*). The chlorides are diminished; a trace of albumin is often present, and occasionally hyaline casts. The amount of acetone is increased; and diacetic acid and other organic acids may appear in some instances. With the excess of coloring-matter in the urine may be taken the fact that in fever there is a progressive decrease of red corpuscles and, according to some writers, a corresponding increase in the amount of iron eliminated in the urine.

The increase of *urea* excreted is one of the earliest changes, and may even precede the rise of temperature. The excess is generally absolute; sometimes it is only relative; that is, more is passed than would be excreted by a healthy man confined to bed on a similar diet. There is usually a marked increase at the commencement of defervescence: this

is most likely due to an accumulation of its precursors in the blood or tissues.

In the **blood**, according to Hayem, both *hæmatoblasts* and *red corpuscles* are less numerous during the stationary period of fever. Directly the fall in temperature begins, the number of hæmatoblasts increases, reaching its maximum a day or two after the disappearance of the fever. During the following week it gradually sinks to normal. An increase in the number of red corpuscles, and a simultaneous diminution in the proportion of hæmoglobin which they contain, closely follow the increase in the hæmatoblasts. The rise in the percentage of hæmoglobin completes the return of the blood to its normal state.

Post-mortem Rise of Temperature.—A slight rise of temperature often occurs after death, especially in those dying suddenly or of acute disease. It is most marked in cases of fever due to the presence of bacterial products in the blood, and in cases where death occurs with a high and rising temperature. Tetanus is probably the best example. The explanation is, that cessation of the action of the heart is not accompanied by immediate extinction of tissue-change. Thermogenic processes continue for a longer or shorter time; and thus, while the production of heat ceases gradually, the loss of heat, being largely dependent on the respiration and circulation, is cut down so suddenly, that the rectal temperature rises for a brief interval, and then falls gradually, as in other cases.

Pathology of Fever.—The foregoing account has shown that the essential condition in fever is increased *thermogenesis* combined with disturbance of the heat-regulating process or *thermotaxis*, whereby the normal balance between heat-production and heat-loss is upset. The thermogenesis is due to increased breaking-down of the tissues and especially of the muscles and the glands. As has been already indicated, by increased thermogenesis is meant that a febrile patient will produce more heat in a given time than a healthy person upon the same diet and under similar circumstances; not necessarily more than a healthy person on ordinary diet, though even this may be the case. The febrile patient takes less food and the increase in heat he produces is due to the excessive combustion of his tissues. Traube held that diminished loss of heat was the principal cause of the raised temperature in the body of a febrile patient, and that this was brought about by an energetic contraction of the vessels of the skin. But such a contraction of vessels is by no means constant, and when it occurs is not of long persistence. Moreover, a high temperature and a freely sweating skin often occur together, and calorimetric observations have actually demonstrated the increased thermogenesis. If support is required for the view that fever is dependent on increased destruction of tissue, it is found in the proportionately increased discharge of urea.

Thermogenesis is under the control of the central nervous system, but in the present state of knowledge it is impossible to speak certainly of the position of the controlling centre, of its function, or of the paths of

its afferent and efferent fibres. It is evident that the causes of fever may induce the increased thermogenesis, either by acting *directly* upon the tissues or by acting on them *indirectly through the nervous system.* In certain cases, *e. g.*, nervous or hysterical fever, it seems impossible that the cause can act upon the tissues otherwise than through the nervous system, but in the majority of cases it may act either way.

It has been shown that thermogenesis may be increased enormously in health without any rise of temperature, and it is therefore believed that fever involves a disturbance of **thermotaxis**, whereby the balance between heat-production and heat-loss is disturbed. If this balance were maintained, as in health, a stable temperature at a higher level than the normal would result. But the chief characteristic of the temperature in fever is its variability. Cold, food, excitement, effort, antipyretic drugs, all affect the temperature in fever much more markedly than they affect the temperature in health. As MacAlister says, the usual daily fluctuation of the temperature in fever shows merely that *all* the thermal processes are not utterly deranged, some which are rhythmic in health remaining so in disease.

Causation.—Fever may be due to *infective* or to *non-infective* causes. The **infective** causes are living organisms, animal or vegetable, which multiply in the tissues of the body and produce poisons (*toxines*). Instances are seen in the group of "acute specific fevers," in malaria, and in febrile diseases in which there is no local inflammation present, at least in the early part of their course. These constituted the old group of *primary* or *essential* fevers. In some (typhus, malaria) there is no local inflammation throughout; but in many an inflammation appears (of throat, nose and eyes, skin, intestine)—too late and often too slight to account for the fever present.

In some cases the fever is *secondary* to a wound through which organisms have gained access to the body—*e. g.*, septic infection, pyæmia, erysipelas, and lymphangitis. There is also a large group of fevers secondary to inflammations (*inflammatory* fevers—*e. g.*, phthisis), all of which are infective. In these "secondary" fevers the fever-producing materials are manufactured by organisms in some definite part of the body, and are thence cast into the blood.

The **non-infective group** includes: (1) *simple traumatic fever*, which ensues upon "simple" injuries (contusions and fractures). It is generally slight and is most probably due to the absorption of fibrin-ferment (and, very likely, other pyrogenic bodies) from the seat of injury: possibly irritation of nerves—by the original injury or by fragments of bone or tissue—may have some effect in causing the fever, though *strong* irritation of a sensory nerve causes depression of temperature. The fever which occurs in aseptic wounds is probably due to the same causes as the simple traumatic. (2) *Septic poisoning* or *sapræmia* is sometimes included in this class. It is due to the absorption of toxines formed outside the body by bacteria which do not themselves enter the blood-stream. Hence the blood is not in-

fective, but the ultimate cause of the fever is as infective as in those of the other group. (3) Rise of temperature and symptoms of fever may be caused by *injuries to the central nervous system*—*e. g.*, hæmorrhage into the pons Varolii. (4) *Nervous (hysterical) fever* is supposed to be due to the defective control of the central nervous system over the regulation of temperature. The rises of temperature which, in children, puerperal women, and other weakly adults, occur from various emotions and other slight causes—*e. g.*, the rise which is so commonly found after an entertainment has been held in a hospital ward—seem to be examples of nervous fever. This form is unaccompanied by the other phenomena of fever (p. 231).

CHAPTER IX.

PARASITES.

A PARASITE is an organism which obtains its food and lodging at another organism's expense, without destroying it and without rendering it service.

Human parasites may be classified according as their habitat is on the surface of the body (*external*) or in its interior (*internal*). Some parasites are *wholly* parasitic; others only *partially* parasitic—*i. e.*, spend only a portion of their life's cycle in the parasitic state. Some parasites seem to possess a considerable degree of option as to their mode of life, remaining in an independent condition for irregular intervals without apparent detriment (*occasional parasites*). Some can exist in or on any one of many species of animal, others in or on only a few or even a single species; while some are limited to one tissue of a single species.

Parasites generally obtain their nutriment easily, and tend to lose such parts as are not essential to life or for propagation. Thus, external parasites retain the organs of locomotion, for active movement is generally necessary to obtain food, to escape from danger, and to effect copulation. Internal parasites, on the other hand, generally lose these organs—teeth, suckers, and cilia alone excepted. Moreover, internal parasites obtain food and oxygen by direct absorption, and tend to lose both alimentary tract and respiratory system. The power of reproduction which parasites possess is enormous. It has been estimated that the common intestinal round worm produces more than 60,000,000 ova per annum.

The effects of parasites may be either *chemical* or *mechanical*. The chemical effects are chiefly exerted by means of toxic products resulting from the growth and excretion of the parasitic organism. These products may lead (1) to general poisoning of the host; (2) to local destruction of tissues; (3) to inflammatory fibrosis; and (4) to various reflex effects. The mechanical effects comprise (1) the blocking of tubes such as gland-ducts, intestine and bloodvessels; (2) pressure upon and destruction of tissues by the mere presence of the growing parasites; and (3) hemorrhage from weakening and rupture, or from direct perforation, of the walls of the vessels.

There is a popular idea that some animal parasites can appropriate to themselves an amount of nourishment which seriously detracts from that usually at the disposal of the host. This effect, however, is at most unimportant.

It will be readily understood that in all local effects, either chemical

or mechanical, the gravity of the results will depend largely upon the importance of the parts and tissues involved. The growth of a hydatid cyst in the liver may produce a tumor many inches in diameter, yet causing comparatively little inconvenience, while a much smaller growth may lead to a fatal result, if it occur at the base of the brain.

ANIMAL PARASITES.

PEDICULI.

Pediculi and acari are the two principal *external pathogenic animal parasites* of importance in temperate zones. The former are wingless insects: the latter are members of the spider class (*Arachnida*).

Three varieties of pediculus are parasitic on man—*P. corporis*, *P. capitas*, and *P. pubis* (Fig. 125). The first two varieties are closely similar, and all three have many points in common. In length they vary from 1mm. to 4mm. The *head* is conical, constricted at its junction with the thorax, and provided with a proboscis, a pair of prominent jointed antennæ, and a compound lateral eye behind each antenna. The *thorax* in the *P. corporis* and *P. capitis* is marked off from the abdomen by a distinct constriction, and carries, in each of the three varieties, three pairs of jointed legs terminating in claws. The number of segments in the *abdomen* varies with the species. The surface of limbs, thorax and abdomen alike is provided with scattered hairs.

The sexes are distinguished from one another by their respective sizes and by their generative apparatus. The males are from half to two-thirds the size of the females. The penis is large and extends over the centre of the dorsal surface of the last three abdominal segments. The last of these segments is rounded. In addition to their larger size, the females are recognized by the notching of the last abdominal segment and by the possession of a ventral vagina. It follows, therefore, that the females are uppermost in copulation. The number of ova produced by a single specimen varies in the different species. The embryos emerge in from five to seven days, and mature in the course of the following fortnight.

The intolerable itching produced by the digging action of the parasites extends beyond the areas immediately affected, and leads to violent scratching of the parts involved, and this again to abrasions in the skin. Into these abrasions cocci grow readily, and in this way pustules and enlarged glands are produced.

1. The **Pediculus corporis** vel **vestimenti** is the largest of the parasitic pediculi (3.5mm. × 1.5mm.). It is grayish and semi-transparent, and possesses well-developed legs which enable it to move rapidly. There are eight abdominal segments. This parasite inhabits the upper margin of the underclothing on the chest. Here it has easy access to the skin, whence it obtains its nutriment. Pushing its proboscis along some duct, it withdraws blood by suction, the point of

Fig. 125.

i parasitic in man. Fig. 1.—Pediculus pubis (female). Fig. 2.—Pediculus pubis (male). 3.—Acarus scabiei, (*f*) female, (*m*) male—to show comparative size. Fig. 4.—Pediculus tis (female). Fig. 5.—Pediculus capitis (male). Fig. 6.—Ova or nits of Pediculus tis. Fig. 7.—Pediculus corporis (female). Fig. 8.—Pediculus corporis (male). These es show the comparative size as well as the distinguishing features: *a*, antennæ; *b*, legs; nis; *d*, notched posterior segment; *e*, eyes; *p*, proboscis; *s*, glutinous sheath surround- air (*h*). × 15.

entry being subsequently marked by a fine hemorrhagic speck. The ova are generally deposited in the clothes, but may be occasionally seen fastened to the hairs growing on the skin of the thorax or abdomen.

2. The **Pediculus capitis** is smaller than the foregoing (2.5mm. × 1mm.). Its color somewhat simulates that of the skin of its host, and thus may be pale, dark, or distinctly yellowish. In this country the sides of the abdominal segments are generally much darker than in the *P. corporis*, which in general appearance it closely resembles. The *P. capitis*, however, possesses only seven abdominal segments. This pediculus inhabits the occipital region of the scalp. Its legs are the least powerful of the three varieties, and its movements are correspondingly less active. The ova (fifty or thereabouts for each female) are fastened to the hairs of the scalp by a glutinous substance. They are flattened at the free end, and are provided with an operculum, which soon falls off and permits the escape of the embryos.

3. The **Pediculus pubis** is the shortest, and, proportionately to its length, the broadest of the three varieties. The antennæ are very prominent. The constriction at the base of the head is very slight, and the division between the thorax and the abdomen is marked only by the position of the legs. Of these the anterior pair are slight, and are used for walking, while the posterior two pairs are very powerful and terminate in strong crab-like claws, enabling the parasite to cling with great tenacity. This pediculus inhabits the pubic hair, rarely straying to more distant parts. It attaches its ova, ten or fifteen in number, to the base of the hair-shaft. These ova are difficult to see.

ACARI.

The only important parasite belonging to this class is the **Acarus scabiei** (*Sarcoptes hominis*) or itch-mite. This minute, tortoise-shaped arachnid is just visible to the naked eye as a white glistening speck: the female burrows in the epidermis, and the male roams over the surface of the skin (Fig. 126). Short hairs or setæ are scattered over its body, which has, on its dorsal surface, rows of spines forming transverse, serrated lines; and on its ventral, eight short conical legs, terminating in long bristles or stalked suckers.

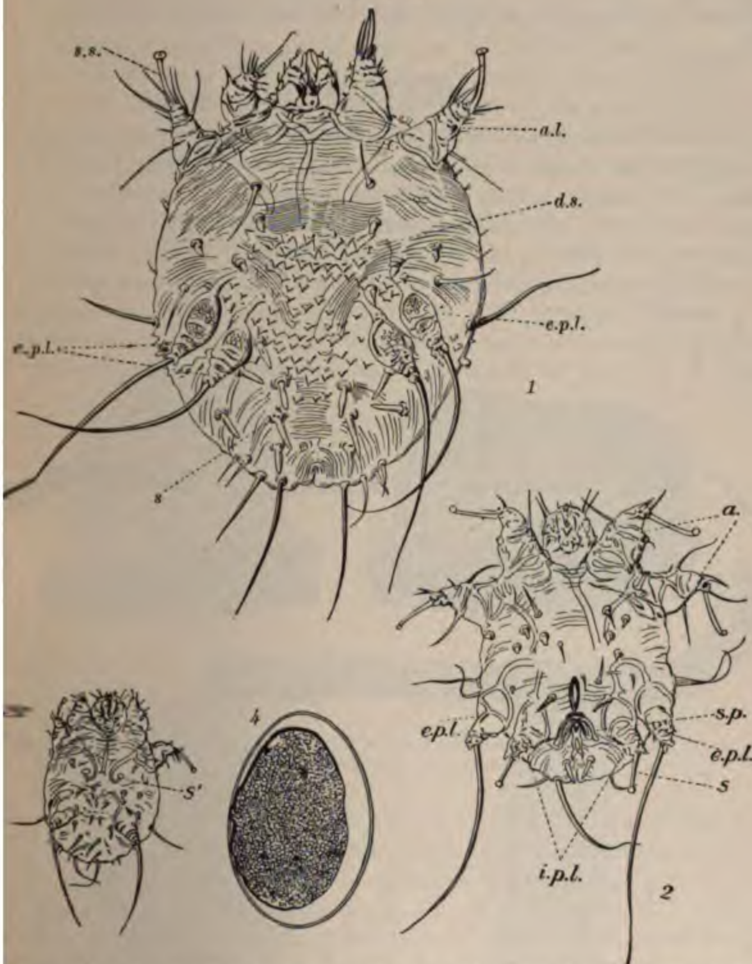
Three features serve to distinguish the female from the male: (1) the size, (2) the distribution of bristles and suckers, and (3) the generative apparatus. (1) The female is rather less than 0.5 mm. long ($\frac{1}{50}$ in.), while the male is rather more than half the size of the female. (2) In both sexes the four anterior legs terminate in suckers. Of the posterior four, in the female, all end in bristles; while in the male, the two *external* end in *bristles*, and the two *median* in *suckers*, an arrangement by which copulation is facilitated. (3) In the female, little evidence of generative organs can be seen beyond the occasional presence of an ovum on the ventral surface; in the male, however, there is a penis, with a horny support, in shape not unlike a pitchfork.

The larval form is smaller than the male (Fig. 126). and possesses

ly six legs. Before reaching maturity it sheds its skin two or three
mes, and develops generative organs and eight new legs. The original
legs are not shed until the new ones are developed, so that in some
ecimens fourteen legs may be counted.

The female acarus burrows into the epidermis, depositing her eggs

FIG. 126.



scabiei. (1) female; (2) male; (3) larva; (4) ovum. *a. l.*, anterior legs terminating in stalked kers (*s. s.*); *e. p. l.*, posterior legs terminating in bristles; *i. p. l.*, posterior median legs of male terminating in stalked suckers; *d. s.*, dorsal spines; *s.*, setæ; *s. p.*, support for penis. 150.

bout one a day—along the track. If undisturbed, she continues to
this for some weeks, and then dies. In the meantime, the ova
adually develop into the larval form, burrow a little, mature, become
pregnated, and finally, in the case of females, start burrowing afresh.

The male does not burrow, but, as the epithelium wears away, reaches, and wanders over, the surface of the skin.

Effects.—The presence of the parasite in the skin gives rise to intolerable itching, which is followed by violent scratching. Pyogenic cocci grow into the abrasions of the skin thus produced and give rise to a pustular eruption. The parasite seems to have a special preference for the hands, feet, and external generative organs. The disease arises from prolonged contact with infected skin, bedding, clothes, or tools.

CESTODA.[1]

The members of the *Cestoda*, indigenous in man, are long, flat, white, tape-like worms inhabiting, in their mature form, the intestinal canal. The mature worm consists of a minute head and neck with a longer or shorter row of attached segments. The complete worm, known as *strobilus*, is, in most cases, not a single individual, but a colony of individuals formed by continual budding from a single spot on a parent segment (Fig. 127). The head or parent-segment is generally 1 mm. to 2 mm. broad, and is provided with suckers which enable it to cling to the wall of the intestine. It is succeeded by a

FIG. 127.

Portions of a Tænia saginata. Natural size. *a*, head, neck, and commencing segmentation; *b*, central; *c*, terminal proglottides.

long narrow neck. At the farther end of this, in the large majority of instances, transverse lines become visible, indicating the divisions between the segments or *proglottides* of which the worm almost entirely consists. Those nearest to the neck are imperfectly developed and defined, those in the centre are distinctly marked off from their fellows and present well-developed generative organs, while those nearest the posterior end are crammed with ova. Each fully developed segment is hermaphrodite. These worms are destitute of digestive organs, and absorb their nutriment directly from the intestinal contents. They possess a complete water-vascular system which takes the form of longitudinal tubes running down each side (Fig. 131).

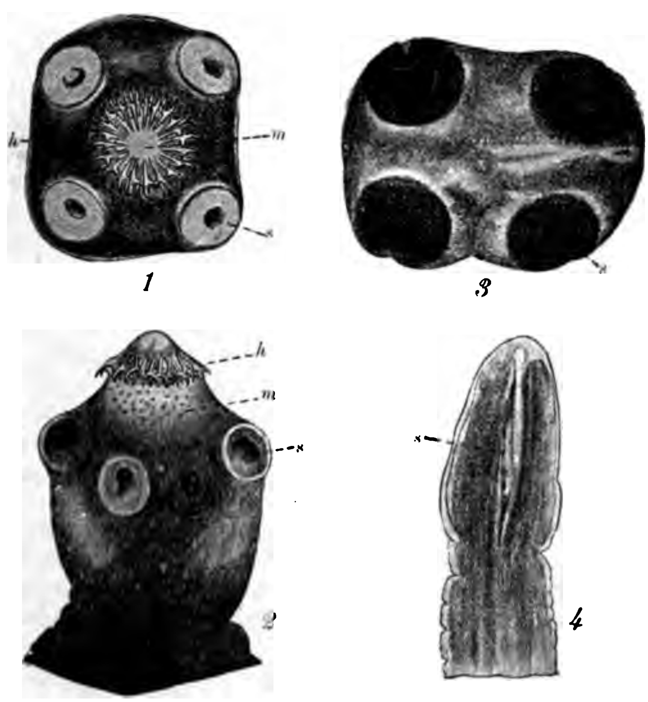
[1] Greek κεστός, a girdle. The Cestodes form a distinct zoological order, and are not in reality *worms* in the strict meaning of the term.

The life history of a tape-worm includes residence in two hosts. The ripe proglottides are broken off, for the most part one by one, from the parent worm. Before they are discharged from the intestine, or even after they have been passed, the ova they contain are set free. It is generally believed that the ova are expelled from the proglottides by the vermicular movements of the latter; in any case they retain their vitality for some days. If at this stage the ova are eaten by some animal capable of acting as the host of the intermediate form of the parasite, they continue their development until the shells are dissolved off in the alimentary tract, and an embryo with six hooklets is set free. By means of these hooklets the embryo is enabled to penetrate the wall of the alimentary tract and, by way of the blood-stream or some other route, to reach some distant part. When the progress of the embryo is finally arrested, the hooklets disappear, and at the end of the embryo opposite to their

FIG. 128.

Tænia saginata. Cystic stage with head everted. × 3. (Ziegler from Leuckart.)

FIG. 129.

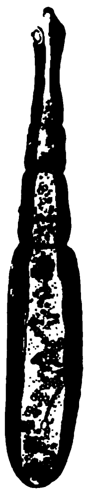


1. Head of Tænia solium, front view. 2. Head of Tænia solium, side view. 3. Head of Tænia saginata, front view. 4. Head of Bothriocephalus latus, side view. *h*, hooklets; *r*, rostellum; *s*, suckers; *m*, summit of rostellum. × 20.

attachment a cavity appears. From the wall of this cavity a fully formed head (*scolex*)[1] develops, while the parasite gradually becomes

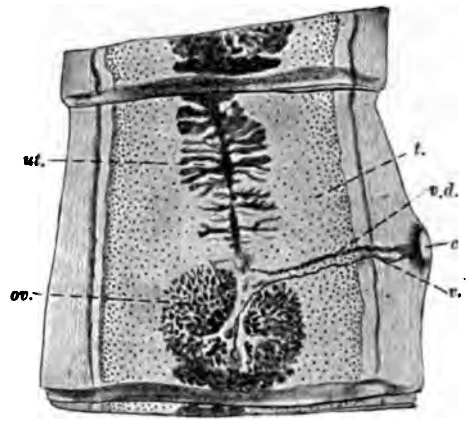
[1] σκώληξ, a worm.

FIG. 130.



Tænia echinococcus. × 12. (Ziegler after Leuckart.)

FIG. 131.



One of the middle segments from a Tænia saginata. *t.*, testes; *v.d.*, vasa deferentia; *ov.*, ovary; *ut.*, uterus; *v.*, vagina; *c.*, genital pore. × 6.

FIG. 132.

Tænia solium. Mature proglottis, with ova. Branching of uterus less complex than in Fig. 130A. × 6.

FIG. 133.

Tænia saginata. A proglottis near the terminal end, showing the female generative organs crammed with ova. *g.p.*, genital pore. × 6.

enclosed in a fibrous capsule supplied by the surrounding tissues. In this *intermediate* or *cystic* stage the parasite, now known as *cysticercus*[1] (Fig 128), may live for many months or may soon die. When dead, it readily undergoes calcification. If, however, tissues containing living cysticerci be swallowed by an animal capable of acting as the host of the mature worm, the investing material is dissolved off, and the scolex is set free. By means of their suckers some of the heads will probably become attached to the wall of the intestine, and segments will quickly develop from the free ends. All new segments are formed at the neck, and the older ones are thus pushed further and further from the head, at the same time gradually developing generative organs. Two months generally elapse between the swallowing of the cysticerci and the passage of the first proglottides from the rectum.

FIG. 134.

Bothriocephalus latus. Three mature segments with coiled rosette-like uterus and central genital pore. × 6.

Four varieties of tape-worm are commonly parasitic in man. Three of these are found in the intestine, the *Tænia solium*, the *Tænia saginata* or *mediocanellata*, and the *Bothriocephalus latus*. The fourth, the *Tænia echinococcus*, does not infest the human intestine, but may be found, in its cystic or intermediate stage, in the liver and other parts. The characters of these four parasites are set forth in the accompanying table, from which it will be seen that, except so far as the head is concerned, the *Tænia solium* and the *Tænia saginata* very closely resemble one another; while the *Bothriocephalus latus* is easily distinguished by the shape of its head, by the breadth of its segments, and by the coil-like form of its uterus (Fig. 134).

Two other tape-worms are less commonly met with in the human intestine, the *Tænia nana* and the *Tænia canina* (*cucumerina*). Of these, the *Tænia nana* is from half an inch to one inch in length, and consists of head, neck, and about 150 broad segments. The head somewhat resembles that of the *Tænia solium*, but is more spherical; while the joints are broad, like those of the *Bothriocephalus latus*; but the genital pore is at the side. The *Tænia canina* is about one foot in length. The head has three or four rows of hooklets, which are twice as numerous as in the other varieties. The segments number

[1] κύστις, a bladder; κέρκος, a tail.

about one hundred, of which the last twenty-five are mature and rather more than a quarter of an inch in length. They have a genital pore on each side of each proglottis. This parasite is most frequently found in dogs and cats, and the intermediate host is supposed to be a tick or louse.

Effects.—These are generally so slight that the presence of the worm is unsuspected until detached proglottides are passed per anum; but slight intestinal colic, and even convulsions and other nervous disorders, occasionally ensue, especially in children. These effects are due either to mechanical irritation or to the absorption of toxic substances formed by the parasites. In the case of *B. latus*, which may be associated with symptoms of profound anæmia, there is some evidence that the parasite secretes a hæmolytic poison.

COMPARATIVE TABLE OF PARASITIC TAPE-WORMS.

SEE FIGS. 125–131.

NAME.	TÆNIA SOLIUM.	TÆNIA SAGINATA.	TÆNIA ECHINOCOCCUS.	BOTHRIOCEPHALUS LATUS.
LENGTH.	7 to 10 feet.	10 to 20 feet.	¼ inch.	10 to 25 feet.
SEGMENTS.	700 to 1000.	1000 to 2000.	4.	3000 to 4000.
HOST.	Man.	Man.	Dog and Wolf.	Man.
Seat.	Intestine, often in numbers.	Intestine, usually singly.	Intestine, in numbers.	Intestine, one or more.
Source.	Infected insufficiently cooked pork.	Infected insufficiently cooked beef.	Infected viscera of sheep.	Infected insufficiently cooked lake fish.
INTERMEDIATE HOST.	Pig: "measly pork."	Ox: "measly beef."	Man and Sheep.	Fish: very rare in United States.
Seat.	Muscle and viscera.	Muscle and viscera.	Chiefly liver, less frequently muscle and viscera.	Muscle and viscera.
Source.	Food infected with dejecta containing ova.	Food infected with dejecta containing ova.	Food infected with dejecta containing ova.	Food infected with dejecta containing ova.
HEAD. (Fig. 125.)	Length $\frac{1}{25}$ inch. Rostellum, 26 or 28 hooklets, double row. 4 suckers.	Length $\frac{1}{12}$ inch. *No* rostellum, *no* hooklets. 4 suckers.	Length $\frac{1}{35}$ inch. Same as Tænia solium, but smaller. 4 suckers.	Length $\frac{1}{16}$ inch. Club-shaped oval, no hooklets. 2 suckers.
SEGMENTS.	Mature segments, length greater than breadth.	Mature segments, length greater than breadth.	4 segments only.	Breadth always greater than length.
GENERATIVE APPARATUS.	*Uterus*, a central canal with about 10 branches. *Papilla*, with genital pore on side of segment; side alternating.	*Uterus*, a central canal with between 20 and 30 branches. *Papilla*, with genital pore on side of segment, alternation irregular.	*Uterus*, a wide cavity in last segment. *Papilla*, with genital pore on side of last segment.	*Uterus*, tube arranged in loops giving appearance of rosette. Genital pore in centre (ventral).
OVA.	Spherical. Almost mature when discharged.	Short oval. Almost mature when discharged.	Spherical.	Oval, with operculum, immature, develop in water, where they swim about.

Hydatid Cysts.

Special reference must be made to the cystic stage of the *Tænia echinococcus*, owing to the frequency with which it is found in the viscera of man, especially in the liver—three-fifths of the total cases occurring in that organ.

The embryos derived from the ova of the adult worm are set free in the intestine, from which they escape, mainly by the veins, and thus reach the liver or other parts where they come to rest. Each embryo is capable of development through a long cycle of changes, the earliest of which consist in the formation of a spheroidal body which gradually develops into a cyst. *The cyst-wall consists of* two layers—an external, transparent, more or less definitely *laminated ectocyst*, and an internal, granular, *germinal* layer or *endocyst* (Fig. 135).

Fig. 135.

Diagram of portion of wall of hydatid cyst, to show development of brood-capsules and scolices. *a*, germinal layer or endocyst showing commencement of brood-capsule; *b*, brood-capsule with two scolices, one inverted, the other everted; *c*, laminated layer or ectocyst. × 50. (Modified from Leuckart.)

The cyst contains (1) a varying amount of *fluid* which is clear, saline, and, in its primitive state, non-albuminous, with a specific gravity varying from 1004 to 1013; and (2) the *scolices* or immature heads of the adult parasite. The scolices differ from the heads of the adults only in the smaller size of the hooklets of the former and in the incomplete development of the roots of their hooklets. There is no complete agreement as to the exact procedure by which these scolices are formed. In all probability they may arise directly from the germinal layer of the original cyst-wall; but more usually they originate from secondary cysts known as "brood-capsules." These are formed as hollow elevations from the germinal layer, and gradually come to consist, as in the case of the original cyst-wall, of two definite layers—though their position is inverted—an outer germinal layer, and an inner imperfectly laminated layer. The outer layer is connected with the original cyst-wall by a stalk (Fig. 135). From the wall of the brood-capsule the scolices are formed, in some cases as invaginated depressions into the interior of the capsule, in others as external projections from the sur-

face. If the wall of the broad-capsules is ruptured the scolices may be scattered unattached through the contents of the cyst. According to Leuckart, all scolices are formed originally from the exterior as hollow buds which, later on, may become invaginated, then appearing as internal projections into the cavity of the brood-capsule. However formed, they may remain quiescent for long periods, or may die and disintegrate (Fig. 136) and become calcified, the calcification of the cyst-walls preceding that of the scolices.

The brood-capsules do not always grow directly from the original

FIG. 136.

Deposit from contents of hydatid cyst. a, scolex; b, scattered hooklets; c, cholesterine crystals. × 100.

cyst-wall, but on some occasions from secondary or daughter-cysts, which may arise as hernial protrusions from the original cysts, or as depressions into its interior. These daughter-cysts may by similar changes produce another generation of corresponding cysts, from any of which brood-capsules may be formed. Sterile cysts, containing neither daughter-cysts nor scolices, are sometimes found, the sterility apparently depending upon the lack of sufficient nourishment. It will thus be understood that the process of formation is very complex and that much room exists for difference of opinion.

The presence of the hydatid cyst leads to the proliferative reaction of the connective-tissue in which it grows, and to the gradual development of an *external fibrous coat.*

Hydatid disease is generally derived from infection of the food or water-supply by contamination with the fæces of dogs, and is commonest, therefore, in those places in which dogs and men are close com-

panions, and where insufficient care is taken to avoid infection. Iceland and Australia are the chief homes of the disease.

NEMATODA.[1]

Nematoda, or round worms, are long, slender and cylindrical, tapering at both ends. They possess a well-developed alimentary tract with a mouth at one end of the worm and an anus at the other. The sexes are distinct, the female being larger than the male. In the male, the genital pore is generally close to the anus, and therefore near the posterior end of the body. In the female, the vagina is near the middle of the abdominal surface. A short description will be given of the principal parasitic forms which are pathogenic in man.

1. **Ascaris lumbricoides.**—This is the common round worm of the intestine. During life it is of a pinkish-gray color with a glistening surface; after death, it loses its pinkish tint and becomes more opaque. The female averages about a foot long and the male six inches. The head has a central mouth provided with three lips. The ova are oval and generally surrounded with semi-transparent albuminous substance. When swallowed, they gradually find their way into the small intestine, developing into the adult form in the course of a month. As a rule, not more than five or six worms are found in the same host. They are especially common in lunatics, negroes, children, and other individuals of dirty habits. Occasionally, however, large numbers may be found in the intestine of a single individual—especially in tropical countries. Although the duration of their life is not accurately known, it is probably not more than a few months. Re-infection from swallowing the ova passed in the fæces may produce a supply lasting some years. The effects of the parasite are due (1) to *irritation*, which gives rise to slight colic and occasionally, in rickety children, to convulsions and other less important reflex effects; (2) to their *wandering habits*, by which the worms may find their way into the bile-duct, stomach, larynx, middle ear, peritoneal cavity, vagina, or other places, and there give rise to symptoms of obstruction or irritation; and (3) to the *matting together*, in a few instances, of several worms, thus causing intestinal obstruction. In the majority of cases the presence of the parasites is unsuspected until they are expelled.

2. **Oxyuris vermicularis** (Fig. 137).—These are small round worms known as *thread*, *seat*, or *maw worms*, having the appearance of shreds of bent or twisted white cotton. The female is one-third to half an inch in length, the male is half this length. The head is pointed and furnished with two cuticular bags, one on the dorsal and one on the ventral surface. The posterior end of the female is long and tapering with a serrated edge, that of the male is curved with a rounded extremity, furnished with a single projecting spike. The ova are of a peculiar and distinctive oval shape, being more convex on one side

[1] Greek νῆμα, a thread.

than on the other, thus taking the form of a bi-convex meniscus (Fig. 138). The ova of the *oxyuris* develop rather more rapidly than

FIG. 137.

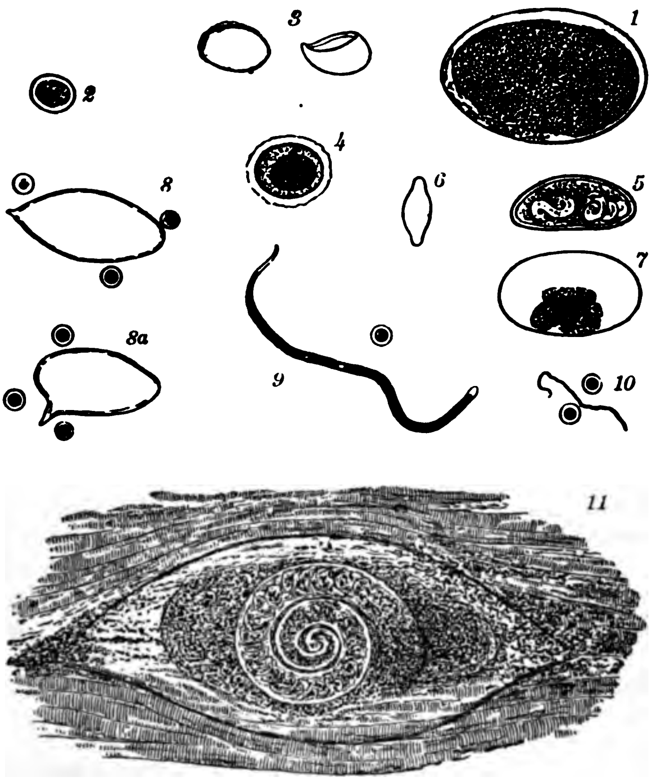
Showing comparative size of various nematodes. 1. Ankylostoma duodenale (female); 1a. Ankylostoma duodenale (female), nat. size; 2. Ankylostoma duodenale (male); 3. Oxyuris vermicularis (female); 3a. Oxyuris vermicularis (female), nat. size; 4. Oxyuris vermicularis (male); 5. Trichina spiralis (female); 6. Trichina spiralis (male); 7. Trichina spiralis, embryos in muscle; 8. Filaria Bancrofti (female), parental form of F. sanguinis hominis nocturna; 8a. Filaria Bancrofti, nat. size; 9. Filaria sanguinis hominis nocturna, embryos in blood. × 14.

those of the *ascaris*, the process being completed in two or three weeks. The ova do not develop unless passed through the stomach. They must accordingly be passed per anum and the host re-infected by the

mouth before a new generation can develop, in cases where any continuous infection is maintained. The oxyurides inhabit the large intestine, especially the cæcum, where they may exist in myriads. As the females become pregnant they generally pass into the sigmoid flexure and rectum.

These parasites are found mainly in children, and are probably

FIG. 138.



Showing comparative size of various ova and embryos. A few red blood-corpuscles have been drawn to serve as a standard of size. 1. Acarus scabiei; 2. Tænia solium; 3. Bothriocephalus latus (one without operculum); 4. Ascaris lumbricoides; 5. Oxyuris vermicularis; 6. Tricocephalus dispar; 7. Ankylostoma duodenale; 8, 8a. Bilharzia hæmatobia; 9. Filaria nocturna (with sheath); 10. Filaria perstans; 11. Trichina in muscle. × 150.

derived from infected vegetables and fruit. Their principal effects are those of local irritation. They give rise to the formation of a large quantity of slimy mucus, some of which is passed with the stools. They may also lead to prolapse of the rectum and enuresis. Their reflex effects are somewhat indefinite. They are accredited with producing cough, restlessness, and even convulsions, though the latter statement is probably erroneous. Their wandering habits are as marked as those of the ascarides, but the results are much less serious. The

females make their way through the anus at night, causing intolerable itching, and may be found in the vagina, on the buttocks, and on the sheets. The itching at the anus leads to scratching and to the deposition of ova under the finger-nails. The additional itching at the mouth and nares, which is also a common effect, leads to the continual transit of the fingers between the mouth and anus during sleep, and accounts for the extreme frequency of autoinfection.

3. **Ankylostoma Duodenale** (*Uncinaria Duodenalis*) (Fig. 137).—This parasite is not endemic in England or the United States, but is exceedingly common in all tropical and subtropical countries. The females are rather more than half an inch, and the males rather less than half an inch in length, but the former are at least twice as thick as the latter. The head is provided with four hooks and two teeth. The posterior end is broad in both sexes, the male possessing an umbrella-like caudal expansion, fitted with ribs and two long projecting spicules. The ova are oval, segmented and enclosed in a thin transparent capsule. They develop rapidly in muddy water and in mould, especially if this is mixed with fæces. The embryos in this stage can exist for months. They are generally supposed to enter their host by the mouth, but it has recently been maintained that their point of entry is the skin, in which they give rise to a form of dermatitis. They take five or six weeks to form fully developed adults. They inhabit the jejunum and duodenum in large numbers, becoming attached to the mucous membrane by means of their hooks, and sucking the blood from the submucous tissue. The results of their presence in the intestine are very variable. In some cases, even when large numbers are present, no symptoms occur: in other cases the parasites give rise to hemorrhage and consequent anæmia, as well as to colic and intestinal catarrh.

4. **Trichina Spiralis** (Fig. 137).—In their fully developed form these minute round worms are, in the case of the female, about one-eighth of an inch long and in the case of the male about one-eighteenth. The head in both sexes is pointed: in the male the posterior extremity is furnished with two jaw-like appendages which probably serve to fix the female during copulation. The ova are hatched within the body of the female and escape from the vagina in the form of minute elongated embryos. The life-history of the parasites can be best understood by tracing the development of the embryos from the intermediate or encysted stage in which they lie encapsuled in the tissues. In this stage they may be found in the connective tissue between the individual muscle-fibres, in the subcutaneous fat, in the wall of the intestine, and in other places. If a portion of muscle infected with these embryos be examined, it will be found to contain a large number of minute oval specks just visible to the naked eye. On microscopical examination each speck is seen to consist of a minute oval capsule with elongated ends, containing usually but one embryo (Fig. 138). These encapsuled trichinæ may live for years. After a time the cyst-wall may calcify:

if the embryo within dies this will undergo the same process (Fig. 139). If a portion of a muscle containing living embryos be eaten by an organism capable of becoming the host, the capsules are dissolved off in the stomach and the embryos pass into the intestine, grow slightly ($\frac{1}{18}$ inch), mature and pair. The female grows rapidly to twice its former size, and develops ova and embryos as described. These are either discharged into the intestinal canal or, according to some observers, are deposited in the lymphatics of the intestinal walls. In any case they reach the muscle and become coiled up within a capsule as previously described. Their complete life-history can be accomplished in about eighteen days—two or three days occur between infection and the pairing of sexes, six or seven more before the embryos are set free, and another nine or ten before they become encysted in the tissues.

FIG. 139.

Calcified trichinæ in muscle. In two of the parasites the capsules and contents are so far calcified that hardly any trace of the coiled embryo remains. In the other the trichina is dead, shrivelled and becoming infiltrated. × 30.

The principal hosts are man, the pig and the rat. The disease is probably conveyed to man in pork—the diaphragm, muscles of the neck, and intercostals being those muscles which contain the largest number of parasites and those which are principally used in the manufacture of sausages. It is obvious, however, that no animal can become infected which is not carnivorous, and it is therefore necessary to explain why the pig should so frequently become infected. The explanation probably lies in the fact that the rat, which is well known to eat its own kind, is very largely infected wherever the disease may be endemic. Thus, successive generations of the parasites are maintained, and pigs may at any time be accidentally infected by eating food containing portions of the diseased rats. With regard to the general subject of infection, it may be noted that, while the adult intestinal trichinæ probably only live for one or two months, the muscle-trichinæ not only live for years, but can resist the decomposition, pickling, and freezing of their environment, succumbing only to a temperature of 80° C., which is rarely reached in the interior of any large joint. The parasite is commonest in America and Germany. Its effects are so marked that they give rise to a definite disease known as *trichinosis*, consisting of two stages. The first stage is characterized by an acute gastro-enteric catarrh due to the presence of myriads of embryos in the intestine, and is sometimes mistaken for cholera or irritant poisoning. This is succeeded by a second stage, which develops when the embryos reach the muscles, and consists of intense muscular pain, swelling, rigidity, and tenderness, giving rise, in addition to a high temperature, to aphonia, dyspnœa, trismus, dysphagia, and other serious symptoms, according to the special muscles mainly involved.

5. Filariæ.—Filariæ are long thread-like worms. In tropical countries many forms are parasitic in the human body. Thus, the *Filaria oculi* is found in the tissues of the eye, and the *Filaria medinensis* (guinea-worm) and the *Filaria loa* in the subcutaneous tissue. All these parasites may produce local irritant effects.

Of greater interest is a group of filariæ known as the *Filaria sanguinis hominis*, because the embryos of the parasites are found in the blood. Of these, the *Filaria sanguinis hominis nocturna* is the best known member of the group.

The adult form of the *Filaria nocturna* is generally known as the *Filaria Bancrofti* (Fig. 137). The female has the appearance of a white thread, about three and a half inches long and rather more than one-hundredth of an inch in diameter. The male is considerably smaller, and less frequently found. The posterior end in both sexes is blunt, and the head slightly bulbous with a central unprotected mouth. The vagina of the female is close to the head. After the death of the host these parasites are generally found in the retro-peritoneal lymph-channels, but may be lodged anywhere. The embryos found in the blood are about one-ninetieth of an inch long, and in breadth equal to the diameter of a red blood-corpuscle. The parasite is provided with a fine sheath which it does not completely fill, and in which it can move backward and forward (Fig. 138). It also exhibits lashing movements, but has no power of travelling from place to place. The embryos are only found in the blood during sleeping hours, hence the name *nocturna*. They appear gradually at about six o'clock in the evening. At midnight they are present in greatest number, and Manson has estimated that there may be as many as 50,000,000 present in the blood of a single individual at that time. They then gradually diminish in number, and by six or seven o'clock in the morning have completely disappeared. During the night some of the parasites may be removed from the blood by mosquitoes. The embryos, which thus reach the stomach of the mosquito, pierce and escape from their sheaths and bore their way into the thoracic viscera, where they undergo further development (Fig. 140). On the death of the mosquito they fall with the body of the insect into drinking water, and thus are conveyed to the stomach of man. Here they develop into a larval form, which escapes from the alimentary tract into the lymph-channels and there develops into the adult form as described above. From this resting-place the female discharges her embryos into the blood-stream by way of the thoracic duct.

Effects.—In most instances of filariasis no effects are observed. In a few cases, however, there may be found associated with the existence of filariæ in the blood (1) an enormous overgrowth of the skin and subcutaneous tissue of the lower extremities, and occasionally of other parts (*elephantiasis arabum*). In these cases but few filariæ can be found in the blood. According to Manson the elephantoid condition is due to the premature discharge of the ova of the filaria. These ova are more than four times the breadth of the embryos and

broader, therefore, than the lymph-channels in the glands through which they cannot pass, and in which, therefore, they are likely to become imbedded. Manson suggests that these ova block the lymph-

FIG. 140.

Filaria sanguinis hominis nocturna. Section through the thoracic muscles of a mosquito about a week after infection with filariæ. In (*a*) and (*b*) the rudimentary mouth and alimentary tract, which are formed during this stage, can be seen. × 90. (From a specimen by Dr. Manson.)

channels in the lymphatic glands one after another, until the whole area drained by the connected lymphatics is engorged with lymph. Overgrowth of the superficial parts follows. The absence of embryos from the blood in these cases is readily explained by the blocking of the channels through which they would reach the blood-stream. (2) In other cases associated with the presence of filariæ, the abdominal, renal, scrotal, and pelvic lymphatics are intensely varicose and filled with chyle, which often finds its way into the urine as well, producing the condition known as "chyluria." The chyle found in these lymphatics can only reach them by regurgitation from the thoracic duct; and, on at least two occasions, the upper part of the thoracic duct has been found blocked. Manson has, therefore, suggested that the first step in the production of chyluria and lymph-scrotum is the plugging or inflammatory occlusion of the thoracic duct, and that the increased lymphatic pressure thus caused leads to a flow of the chyle back through the pelvic lymphatics to those on the abdominal wall, the lymph thus reaching the blood-stream through anastomoses between the lymphatics of the upper limbs and those of the lower. Thus, the presence of chyle in the pelvic lymphatics may be accounted for, while the rupture of varicose lymphatics thus produced suffices to explain the existence of the chyluria.

Several other varieties of the *Filaria sanguinis hominis* are described. The *Filaria diurna* in its embryonic form closely resembles the *nocturna*,

differing from it only in the time at which it appears. The parental form of the *F. diurna* has not been described, but Manson suggests that the *Filaria loa* may really occupy this relationship. The embryos are not pathogenic.

The *Filaria perstans* is a thinner and shorter embryo than those before mentioned (Fig. 138). It has no sheath, possesses rapid movements by which it travels from place to place, and is never absent from the blood of an infected individual. The majority of the natives on the West Coast and in the central parts of Africa seem to be infected with it.

TREMATODA.

Several members of this order are on rare occasions found as human parasites. Thus, the *Distoma hepaticum*, or parasite of sheep-rot, and the *Distoma lanceolatum* are occasionally found in the liver. The only species commonly parasitic in man is, however, the *Distoma hæmatobium* or *Bilharzia hæmatobia*. The female has the form of a thin thread an inch long; the male is half an inch long, of milk-white color, flat, and curved laterally so as to be slightly concave on the ventral side (Fig. 141). During sexual intercourse the curve increases so that the opposite sides meet to form a "gynæcophoric canal" in which the female is enclosed. At the anterior end of the male there are two suckers.

FIG. 141.

Bilharzia hæmatobia, male and female. The small figure on the left shows a transverse section of the two worms *in situ*. × 20. (After Sandwith, from Looss.)

These parasites, especially the males, are found in large numbers in the genito-urinary and mesenteric veins of infected persons. After impregnation the females are believed to move into the smallest vessels and there to discharge their ova. In shape these are generally compared to a melon-seed, being pointed at one end (spike) and enclosed in a transparent membrane (Fig. 138). Their contents often appear segmented, and occasionally the different parts of the future embryo can be clearly made out. They very rapidly mature in pure water, the membrane rupturing and setting free a somewhat elongated embryo provided with cilia. The eggs do not mature, and the embryos are never set free, either within the bloodvessels or in the urine. Sometimes the spike is placed on one side of the ovum (Fig. 138), and this arrangement is caused by immaturity of the female which produces the egg.

[1] τρῆμα, an orifice.

The period which may elapse between infection and the appearance of ova in the urine is variable, but never less than four months. The parasite is chiefly found in Egypt, Arabia, and South Africa. The exact method of infection is unknown. The embryos are probably introduced with drinking water, though a few authorities still maintain that local infection along the urethra may occur during bathing. Entrance through the skin is not at all improbable.

The effects of the parasite are to produce vesical and perineal pain with dysuria. Ova may be found in the urine, which frequently contains blood, especially toward the end of micturition. The ova may lead to the formation of clots in the bladder, and subsequently to the formation of calculi; while in the tissues chronic inflammation may occur in the neighborhood of both parasites and ova.

PROTOZOA.

Amœba coli is the name applied to a minute parasite (three to five times the diameter of a red blood-corpuscle) occasionally present in healthy fæces, and frequently in those in dysentery. It also occurs in the pus of liver-abscesses in a large proportion of cases. By appropriate staining of hardened sections the amœba, in suitable cases, can be demonstrated in the tissues constituting the floor of the dysenteric ulcer or the walls of the liver-abscess. In fresh fæces and pus it can be detected with a magnifying power of 100 to 200 diameters in compressed films examined on the warm stage. The parasites are recognized as colorless, or very faintly green, actively amœboid bodies creeping about by means of rounded pseudopodia. Should the temperature of the slide fall much below blood-heat, amœboid movement ceases and the organism assumes a spherical form, but the amœboid movement is again resumed on warming up the slide a second time. In certain instances the spherical form persists at all temperatures. In liver-abscess the amœba is most readily found in the pus coming from the drainage-tube

FIG. 142.

Amœba coli. Some leucocytes are shown between the amœbæ. (Modified from Lösch.) × 320.

some days after operation. It is more difficult to find, and may not occur, in the pus evacuated at the time of operation. The explanation lies in the fact that the habitat of the amœba is the granulation-tissue forming the wall of the abscess.

The amœba consists of a grayish, slightly granular central portion —endosarc—in which a nucleus and one or more minute vacuoles can be detected, and a peripheral hyaline portion from which the pseudopodia are mainly formed—ectosarc (Fig. 142). In many instances blood-corpuscles, bacteria, and débris of all kinds can be seen included in the parasite.

There is great difference of opinion as to the pathological significance of the amœba. Some hold that it is merely an accidental occurrence, others that it is the cause of certain types of dysentery—*amœboid dysentery*—and of liver-abscess. As yet the clinical and experimental data do not warrant a definite opinion on these points.

HÆMATOZOON MALARIÆ.

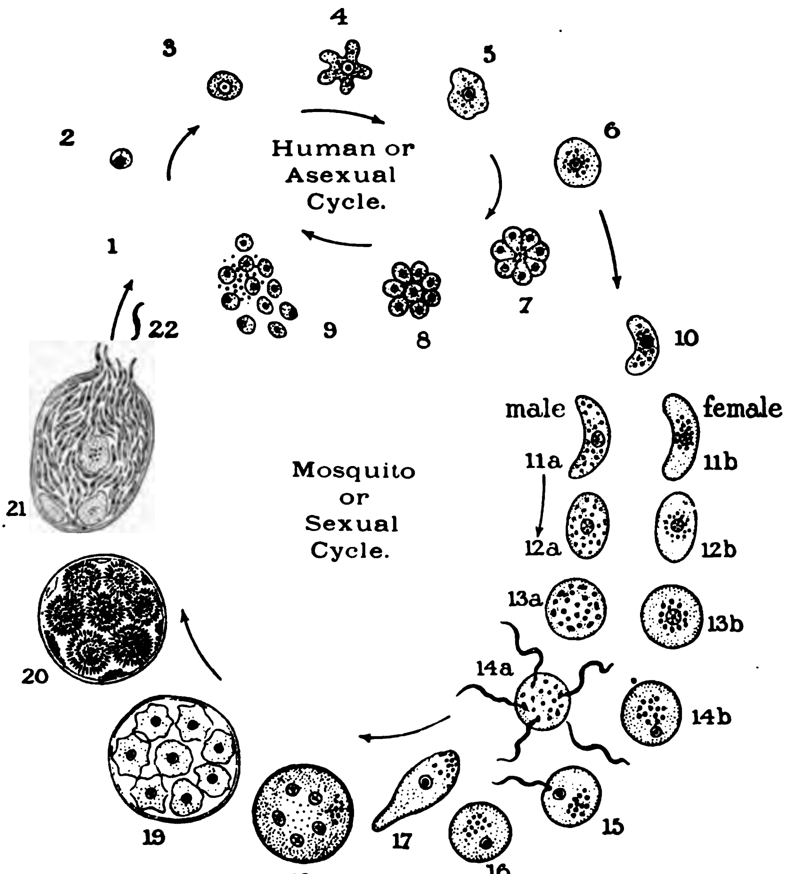
Malaria is the name which for many years has been employed to denote the virus of a frequently fatal disease, occurring principally in tropical climates, and characterized by periodic attacks of fever. When these attacks recur *daily* the disease is known as *quotidian* ague; when on *alternate* days, as *tertian* ague; when every *third* day, as *quartan* ague. The periodicity is not always so regular or so simple, nor are the intervals so short, as in these examples. When the individual febrile recurrences run into each other, so that there are no apyretic intervals, but only slight remissions, the term "remittent fever" is applied to the attack. The anatomical changes met with in the disease are great enlargement of the spleen and marked pigmentation of many parts—*e. g.*, spleen, liver, and brain. It is the type of an *endemic disease:* it is strictly limited to particular localities; that is to say, it can be acquired in these localities only, although its clinical manifestations may develop elsewhere. It is never communicated directly from person to person, except by the direct intravenous inoculation of blood taken from an individual in whose blood the germ is present.

Laveran first pointed out that if a careful examination be made of a drop of blood taken from a malarial patient during, shortly before, or, in certain types of the disease, some time after, one of these febrile attacks, certain characteristic appearances will be found. These are:—(*a*) Circular or ring-shaped amœboid disks, pale and apparently structureless, lying on or in the red corpuscles, and not unlike vacuoles (Fig. 143, 2, 3); (*b*) pigmented amœboid bodies occupying from a sixth to almost the whole of the affected corpuscle, which usually contains only one such body (4, 5); (*c*) well-defined rosette-shaped or clustered bodies, the segments surrounding or radiating from a clump of pigment in or about the centre of the figure (7)—these may be free in the plasma or may be encircled by the remnant of a red corpuscle;

(*d*) pigmented crescentic bodies (10, 11); (*e*) flagellated organisms and free flagella (14a, 15); (*f*) leucocytes containing black pigment.

It is now proved that the appearances seen in the blood-corpuscles

FIG. 143.



Scheme of life-history of malarial parasite. The upper circle (1-9) shows the development within the human body; the lower circle shows the changes which occur within the body of the mosquito (10-22): 1, blood-corpuscles, ready to be infected by either merozoites (9) or sporozoites (22); 3-6, development of amœbula within blood-corpuscle; 7, 8, division of amœbula into merozoites, which are finally set free in the blood (9); 10, crescentic body developed from parasite within blood-corpuscle, after this (6) is swallowed by mosquito; 11*a*, 11*b*, male and female forms (crescents); 12*a*-14*a*, development of male gametocyte; 12*b*-14*b*, development of female gametocyte; 14*a*, formation of flagella or male gametes. 14*b*, female gamete after casting off polar body which is shown lying beside it; 15, fertilization or conjugation; 16, zygote; 17, oökinete or travelling vermicule; 18, 19, formation of sporoblasts; 20, formation of spores or sporozoites; 21, discharge of spores into body-cavity of mosquito; 21, free spore leaving salivary gland to enter human host.

represent different stages in the life-history of a parasitic organism, or rather of a group of organisms, since a different species is associated with each of the varieties of malaria—tertian, quartan, and malig-

nant. These organisms, which belong to the class of *Sporozoa* (Order, *Hæmosporidia*), go through a cycle of changes within the human host. If, however, the infection is not renewed, they tend to die out after a time. In order that their vitality may be restored it is necessary that they should enter the body of a different animal—the mosquito—and therein carry out the process of conjugation, or union of two individuals representing respectively male and female elements. Infection of a second human being or re-infection of the original host is then effected by the bite of the mosquito.

The cycles of development undergone by the malarial parasite within the human body and in the mosquito are diagrammatically represented in Fig. 143.

Human Cycle.—If we start at the moment of infection by the bite of the mosquito, we see that a minute, rod-shaped body (Fig. 143, 22) is conveyed into the human blood from the insect's proboscis. This little rod or spore immediately proceeds to enter one of the blood-corpuscles of the new host, and within the corpuscle it goes through the following series of changes. It first enlarges until it may occupy the greater part of the corpuscle (2–6). Then segmentation takes place: the nucleus first divides, and its fragments take up positions at the periphery of the organism; then divisions appear in the protoplasmic substance between these daughter-nuclei, and the parasite divides into segments (7). Each of these segments now assumes a rounded form, so that the blood-corpuscle contains a number of small round bodies (*merozoites*) (8); and by the death and rupture of the corpuscle these are set free in the plasma (9), the shrivelled remains of the stroma of the corpuscle being sometimes visible in the blood as the "brassy bodies" of the Italian writers. Each spore next proceeds to invade a fresh blood-corpuscle; it there enlarges to adult size, and the process of segmentation begins again.

It is found that all of the parasites resulting from a single infection enter on the stage of sporulation at the same time, and that the simultaneous setting-free of the merozoites into the blood-stream corresponds in point of time with the access of fever in the patient; taking place every third day in the case of the tertian parasite, every fourth day with the quartan parasite, and irregularly with the malignant organism. It must be assumed that on rupture of the blood-corpuscles some poison is liberated which is capable of exciting pyrexia.

By the destruction of the corpuscles a quantity of dark pigment is produced, and this is set free in the blood-stream. Some of it is deposited in the spleen and liver, which become deeply pigmented; while other granules are ingested by leucocytes. Pigmented leucocytes are very characteristic of the blood of malarious patients, and the discovery of them may aid in the diagnosis of the disease.

Mosquito Cycle.—When a mosquito, of the genus *Anopheles*, bites a human being who is the subject of malaria, it takes into its stomach some blood-corpuscles containing adult organisms (6, 10). These proceed to develop on lines differing from those pursued within the

human host. The corpuscles are dissolved, and the organisms escape. These take on male and female characters (*gametocytes*). In the male (Fig. 143, 11a) the nucleus divides into a number of small fragments, arranged round the periphery of the protoplasm, and from each of these a long protoplasmic process or flagellum is extruded (14a), closely resembling in form and attributes a spermatozoön. The flagella break off from the body of the parasite, and each proceeds to conjugate with a female organism, just as a spermatozoön unites with an ovum (15). Meanwhile the female organism (11b) has prepared for conjugation by throwing off a polar body and forming a micropyle for the entrance of the head of the male element (14b). After conjugation has occurred the nuclei of the male and female elements fuse, and the resulting organism becomes sharply pointed at one end. It is now called the "travelling vermicule" or "oökinete" (17), and proceeds to burrow through the wall of the mosquito's stomach (Fig. 144). Arrived within the tissues, it undergoes further changes: the nucleus divides into a number of fragments, and the protoplasm becomes arranged round these, forming rounded masses or sporoblasts (19). By fresh fragmentation of the nuclei and protoplasm of these sporoblasts a number of rod-shaped spores are formed, all adherent at first to a remnant of the sporoblast which has not divided (20). These spores are finally set free in the tissues of the mosquito, enter its salivary gland, and are ready to be injected into a human host whenever the insect bites. When infection is thus transmitted the human cycle of the parasite takes place as already described.

FIG. 144.

Stomach of mosquito, showing cysts of malarial organism in the wall. (After Ross.)

The hypothesis originally framed by Manson as to the conveyance of the infection of malaria by means of mosquitoes has now been fully confirmed. In India, Ross fed certain species of mosquitoes on birds in whose blood an analogous parasite was present, and, on subequently causing these mosquitoes to bite healthy birds, found that the latter became similarly infected. Bignami and Grassi obtained similar results with human malaria, while Ross demonstrated the existence of the parasite within the body of the mosquito.

The name *Plasmodium malariæ* is now confined to the organism of quartan ague; that of tertian ague being called *Plasmodium vivax*, and that of pernicious or æstivo-autumnal malaria *Laverania malariæ*. These three species differ somewhat in appearance and life-history. The peculiar crescentic forms of gametocytes shown in Fig. 143 are only met with in the case of *Laverania*, the intracorpuscular stage of which is often ring-shaped. *Plasmodium vivax* exhibits very active amœboid movements; the other forms move less rapidly. Corpuscles attacked by *Plasmodium malariæ* shrink in size, whereas those containing *P. vivax* become swollen and pale. In pernicious malaria the organisms may be found in large numbers in the cerebral capillaries which

they appear almost to block; the severe symptoms of this form of the disease may be associated with this localization of the parasites.

The administration of quinine is followed by the disappearance of the intra-corpuscular parasites; the crescentic bodies are the last to go. Leucocytes have been seen to approach and touch corpuscles containing the parasite, though they never *enclose* any but the extra corpuscular forms.

Trypanosoma.—These minute flagellated organisms (Fig. 145) are responsible for the disease known as trypanosomiasis and probably for sleeping sickness (African lethargy). The parasites are worm-like in shape, and possess a macronucleus and micronucleus. A long flagellum with which the organisms are provided is apparently continuous with the micronucleus. Between the flagellum and the body of the organism there extends a fine transparent membrane (undulatory membrane). Trypanosomes multiply by fission. Schaudinn, however, finds that a species resident in owls exhibits spore-formation, passing through stages very similar to those of the malarial organism. He therefore classifies the trypanosomata among the sporozoa. He further believes that the organism of relapsing fever, hitherto regarded as a spirillum—a vegetable organism—is a stage in the life history of a species of trypanosome. It is uncertain whether the trypanosome discovered in patients suffering from sleeping sickness by Castellani, and considered[1] to be the cause of this disease by Bruce and Nabarro, is the same as that found in cases of trypanosomiasis, and whether the latter malady is merely a preliminary stage of the former. The parasite is probably conveyed to human beings in the case of sleeping sickness by the bite of a species of fly, *Glossina palpalis*.

FIG. 145.

Trypanosoma, from a case of sleeping sickness. (After Bruce and Nabarro.) × 1800.

Certain peculiar bodies found in the spleen of patients suffering from a form of fever endemic in India, and named after their discoverers "Leishman-Donovan bodies," are probably a stage in the development of a trypanosome. Some authorities, however, regard these as a different species of parasite (*Piroplasma*).

The Organism of Small-pox.—Councilman and his assistants have described in cases of small-pox peculiar bodies which they regard as protozoa and which they believe to be the cause of the disease. The "organisms" are described us undergoing a double cycle of development within the human host. They appear first in the protoplasm of

[1] A peculiar streptococcus has been found in patients suffering from sleeping sickness; it is probably due to a "terminal" infection.

epithelial cells and there break up into spores. These proceed to invade the nuclei of the tissue-cells, and to undergo a second segmentation. The nature of these bodies is still uncertain: they are recognized as protozoa (*Cytorrhyctes variolæ*) by Calkins.

VEGETABLE PARASITES.

Fermentation and Infective Disease.—It has long been thought that the group of acute specific diseases must have a special cause. The characteristics of this group are: (1) that they occur in epidemics; (2) that they are obviously contagious and infectious; (3) that each member is absolutely distinct from its fellows, and runs a typical course; and (4)—the most important distinction of all—that the poison which gives rise to each of them multiplies in a marvellous manner. Thus the introduction into a community of a single case of one of these diseases may be followed by the death of thousands from the same malady. For a long time nothing could be discovered to account for the appearance of these diseases, though they were obviously produced by something which multiplied in the patient, which clung about his clothing, and which could be carried through the air for considerable distances. This "something" was, and still is, called the "*contagion*" of the disease. It was at the outset recognized that no gas could be a sufficient cause, for diffusion would soon put an end to its power for mischief. A fluid was still more out of the question. *Contagion* was, therefore, necessarily regarded as a solid in a state of very fine division—*particulate.* This view was confirmed by the discovery that it could be removed from fluids, both by subsidence (vaccine, Chauveau) and by filtration through porcelain—the poison not passing through the filter. These facts, taken with its power of multiplication, seemed to show that the contagion was some living organism, hence the origin of the *contagium vivum* or *germ-theory* of disease. In 1840, Henle clearly formulated the doctrine that living organisms, probably of a vegetable nature, were the causes of the acute specific fevers, and supported the view by arguments which have withstood all endeavors to refute them.

Long before 1840, however, it had been noticed that a close parallel might be drawn between an infective disease and a fermentation. It may be presented thus:—

Infection	Addition of ferment.
Incubation	Period during which nothing is noticed.
Fever, outbreak, and course of disease	Rise of temperature, and active fermentation.
Decline of disease	Gradual cessation.
Period of protection from same disease	Addition of more ferment has no effect.

The discovery by Pasteur of the fact that fermentation is due to the action of micro-organisms strengthened the evidence in favor of a parasitic cause of infectious disease.

The first organism identified as the exciting agent of a disease was the bacillus of anthrax or splenic fever, discovered by Davaine (1850).

After this the progress of discovery was rapid; bacteria are now proved to be the causal agents in a large number of infectious diseases—anthrax, diphtheria, tetanus, tuberculosis, enteric fever, plague, cholera, leprosy, influenza, Malta fever, pneumonia, gonorrhœa, erysipelas, and suppurative conditions—and in many others their causal connection is highly probable.

Proof of the Relation of Micro-organisms to Disease.—To prove that a micro-organism is the cause of a disease, it is necessary that the following conditions should be fulfilled ("Koch's postulates"):

1. That the organism in question, as recognized by its form, mode of growth, or products, be found constantly associated with the disease, at least in its earlier stages; and in sufficient numbers to account for the symptoms.
2. That "pure" cultivations of this organism through several generations be made, until it may reasonably be supposed that everything which could possibly have been taken from the animal that yielded the virus has disappeared.
3. That other susceptible animals be inoculated with the cultivated organism, and that the disease be thus reproduced.
4. That the same organism be found in the tissues of the successfully inoculated animals in such numbers and with such a distribution as to account for the disease.

Sidney Martin has suggested that the chemical products of the organism, obtained from the tissues of the animal or person dead of the disease, must correspond with those obtained from culture of the organism in media resembling as nearly as possible in chemical composition those tissues in which the organisms are found in disease; but owing to the impossibility of ensuring that artificial media shall at all closely resemble vital fluids, it is clear that it is impossible to insist upon such an identity of products.

The demonstration of a *well-characterized* organism in *constant* association with a disease is now by many taken as almost equivalent to proof that it is the cause of the morbid process, for it is in most cases impossible to experiment on man, and frequently no animal can be found which suffers from the disease under investigation. In such cases the proof cannot be carried beyond the first stage.

The vegetable organisms which have been found connected with the diseases of man (pathogenic) belong to the class of *Fungi*. The parasitic fungi are of three kinds—**Bacteria** or *Schizo-mycetes*, **Yeasts** or *Blasto-mycetes*, and **Moulds** or *Hypho-mycetes*.[1] The bacteria include the causes of putrefaction and several of the "fermentations," as well as most of the organisms which are believed to produce the infective disease. They are, therefore, by far the most important group.

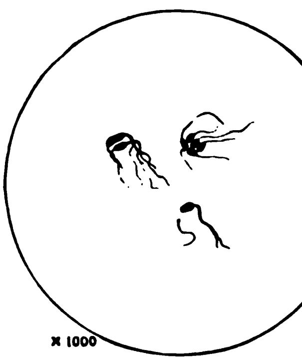
[1] Greek σχίζω, I split; βλαστός, a sprout; ὑφή, a thread; μύκης, a fungus.

I. BACTERIA OR SCHIZO-MYCETES.

Morphology and Life-history.—The Schizo-mycetes or Fission-fungi are, with very few exceptions, non-nucleated, unicellular organisms which do not contain chlorophyll. Many of them approach the limits of microscopic visibility, whilst all are very minute, the smallest diameter of a pathogenic bacterium rarely exceeding 1 μ ($\frac{1}{25000}$ in.). It is highly probable that the causal agents of some diseases are so minute as to be invisible even with the highest powers of the microscope. It has been proved that the virus of certain infective diseases is capable of passing through the pores of a Chamberland porcelain filter.

Form.—In form they may be said to follow, more or less closely, one of three types—the *sphere*, the *rod*, and the *comma*. The *spherical* bacteria comprise those of any shape between a sphere and a cube. The *rod-shaped* bacteria may be short and thick with rounded ends, so as closely to approach an oval; or they may be long and thin with square ends; or they may exhibit any possible combination of these features. The *commas* in some cases are long and thin, in others short and thick: they differ also in their degree of curvature. *Spiral* and *dumbbell* forms are less common. Among the higher bacteria more complex forms obtain. Long septate and non-septate filaments are found. These may undergo false branching or true branching (p. 269).

FIG. 146.



"Blue milk" bacilli—stained by Lœffler's method to show flagella. × 1000.

Structure.—Bacteria appear structureless. They consist of a peculiar form of protoplasm, known as *myco-protein*, the composition of which varies in different species. It is probable, from their great resistance to alkalies and dilute acids, that bacteria possess a cell-membrane formed of some carbo-hydrate allied to cellulose. During the formation of spores, and after the action of tincture of iodine, which stains and causes shrinking of the protoplasm, a fine membrane may be actually seen. It is very elastic, and seems to form the inner layer of a gelatinous envelope, by more or less of which all bacteria are surrounded.

Color.—Bacteria refract light strongly, and cause turbidity of any culture-fluid in which considerable numbers are present. Apart from artificial staining, a mass of organisms is usually colorless—*i.e.*, white or grayish. Some bacteria are brightly colored, red, blue, yellow, etc., the tint being mainly in the envelope. Bacteria are stained with more or less facility by several aniline dyes, and many of them may be identified by their special staining reactions. The substance of the bacterium does not always take the stain uniformly throughout. This irregularity depends on spore-formation, on degenerative changes, or on

the results of osmosis. It generally indicates that the organisms have been reared under unfavorable conditions. Some forms are stained brown by iron salts in water. The starch reaction with iodine is not rare.

Movement.—Some rod-forms are motile—*e.g.*, *B. typhosus*, *B. tetani*: some never move—*e.g.*, *B. anthracis*, *B. tuberculosis*. In most motile bacteria, when specially stained, one or more cilia-like filaments or *flagella* have been found. These seem to be connected not with the cell-membrane, but with the protoplasm. In some organisms one or more flagella are found at one end only; in others, as in the cholera-spirillum, they may grow from both ends (Fig. 146); and in a few, among them the typhoid-bacillus, they are very fine and are attached all around (Fig. 147). By means of these flagella, movement is probably effected. No motionless bacterium is provided with flagella, though on a few motile forms none has yet been found.

Some bacteria have a motile stage and a motionless stage. In these cases motility can often be induced by varying the medium and

FIG. 147.

Typhoid bacilli—stained by Van Ermengem's method to show flagella.

the temperature. In some, motility occurs just before division; in others, shortly afterward.

Living bacteria are subject to attraction by certain substances (*chemotaxis*, p. 179). Thus typhoid-bacilli are attracted by potato-juice. A good supply of oxygen seems to be necessary for the active motion of some forms.

Reproduction by Fission.—All bacteria multiply by transverse division. In the rod-forms this occurs in a direction at right angles to the long axis. In the spherical forms it may take place in two or in three directions, at right angles to each other. Thus, one cell may divide by a single act of reproduction into two, four, or eight equal segments. If division occur in two or more parallel planes before the separation of the segments takes place, the number of these will be largely and proportionately increased (Fig. 148, *c*). A cell, which

divides in a single plane, elongates as it divides, so that the progeny retain the proportions of the original parent-cell.

FIG. 148.

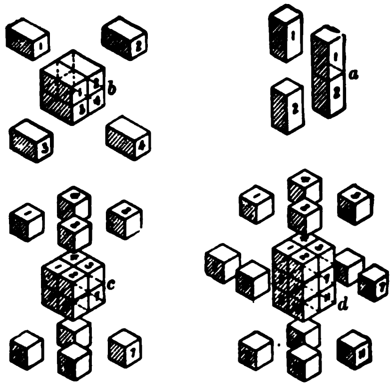
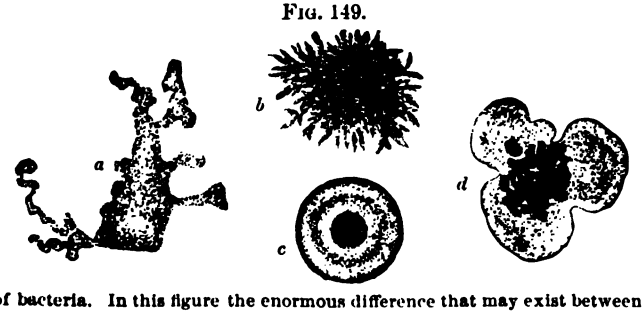


Diagram to show methods of reproduction by fission. *a*, fission in one direction—the segments lengthening as they divide; *b*, fission in two directions—each segment subsequently divides in the same direction as in *a*; *c*, fission in three directions—in one direction division takes place in two parallel planes; *d*, fission in three directions.

The new cells formed by fission may at once separate from the parent, or they may for a time remain united to each other, end to end. In this way pairs or chains of cocci and long filaments of rods are formed. A mass of organisms lying side by side in more or less spherical colonies, and bound together by a viscid substance, formed of swollen cell-membrane or of mycoprotein, is known as a *zoöglœa.*[1]

FIG. 149.



Colonies of bacteria. In this figure the enormous difference that may exist between the grouping of one mass of organisms and that of others is shown. (After Sternberg.)

Zoöglœæ often combine to form constant characteristic appearances by which the organism may be recognized, even by the naked eye (Fig. 149).

The time occupied in division varies in different species from ten to thirty minutes; and, as the offspring proceed at once to divide like their parents, a single bacterium may, in twenty-four hours, give rise to more than 16,000,000.

[1] Greek, ζῶος, living; γλοια, glue.

Reproduction by Spores.—Another method of propagation, or, more correctly, state of existence (*resting stage*), is met with among the fission-fungi—namely, the formation of spores. Spore-bearing organisms have been divided into two groups—*endosporous* and *arthrosporous*.

(1) The *endosporous group* consists of certain long rod-forms (*bacilli*) and some spiral forms. The spore first appears as a minute point in the cell, enlarging rapidly, and often attaining maturity in a few hours. It is then a clear, round or oval, highly refracting body, which has evidently grown at the expense of the cell-contents; the latter gradually disappear (Fig. 150). A spore consists of protoplasm and fat enclosed in a firm capsule. It is quite exceptional to find more than one spore in a single segment. Spores are extremely resistant to unfavorable surroundings, owing, apparently, to the qualities of their fine limiting membrane. Spore-formation only takes place under special conditions, which are generally not those altogether favorable to growth and multiplication. But it can hardly be regarded as evidence of lowered vitality, for spore-formation in anthrax-bacilli can be arrested by reducing the temperature of the organisms below 20° C. or by introducing certain modifications into the culture-media. Fission and spore-formation may go on together.

FIG. 150.

Bacillus anthracis, showing spore-formation in bacilli and free spores. × 1000.

If after long periods of quiescence spores are placed in favorable conditions, germination takes place: their capsule bursts and is shed, they lose their fine dark outline, and the new adult (*vegetative*) cell grows out—usually in the direction of the long axis of the spore.

(2) In the *arthrosporous group* no spores are found within the cells, but certain cells, during the process of division by fission, exhibit unusual powers of resistance, and are, therefore, regarded as spores. Sometimes these arthrospores are larger than the rest of the cells: in other instances no difference in appearance can be made out.

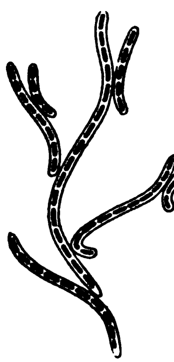
Some authorities hold that all micrococci and microbacteria are examples of the second variety. No distinction can, however, be drawn between the early and late stages of cocci, and it is better, therefore, not to include spherical forms among spore-bearing organisms.

Many bacteria are *monomorphic*—that is, each individual organism, from the beginning of its existence to the end, preserves the same form. Slight inequality in the size and form of the cell is the only variation that such organisms present. Others are more or less *pleomorphic*—*i. e.*, in their life-history, spores, rods, filaments, and zoöglœæ can be traced, co-existent, or succeeding each other.

Classification.—Until recently, the possibility of the variability of bacteria was much discussed. It was considered by some observers

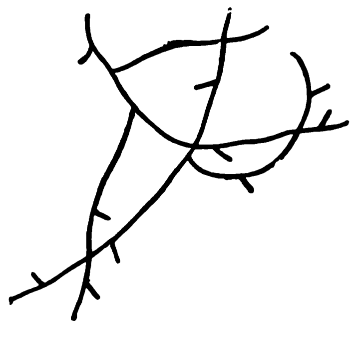
that many bacteria, differing in shape, characters and pathogenic effects, and hence regarded as belonging to different species, were really only modifications of a single form. It is, however, now generally agreed that no kind of bacterium, however nearly it may resemble another, ever becomes converted into it; *e. g.*, the smegma-bacillus is never converted into the tubercle-bacillus, nor the Bacillus coli into the Bacillus typhosus. Certain characteristics may be for a time modified: the virulence, as has been pointed out, is liable to much variability; and the capacity to form spores may depend upon the temporary environment.

FIG. 151.



Cladothrix dichotoma, showing false branching. × 1000.

FIG. 152.



Streptothrix actinomyces, showing true branching. × 1000.

Notwithstanding the general agreement on the individuality of the various forms of bacteria, our knowledge is still too limited to enable us to classify them with any pretence to accuracy. The simpler forms are spoken of as (1) *cocci*, (2) *bacilli*, and (3) *spirilla*—the classification depending on their roughest morphological characters.[1] The more complex bacteria, which form the connecting link with the higher forms of fungi, are sometimes classified according to the structure of the filaments, the appearance of the protoplasm, and the existence of branching. Thus, Muir and Ritchie classify freely moving septate filaments, containing sulphur-granules as members of the Beggiatoa group; similar filaments, fixed at one end and developing from the

[1] The following terms are often used to describe varieties of bacteria:

Cocci and micrococci	. Spherical or nearly spherical bacteria.
Diplococci	. Cocci in pairs.
Streptococci . . .	. Cocci in chains.
Staphylococci . . .	. Cocci in groups like bunches of grapes.
Tetrads	. Groups of four cocci produced by imperfect cleavage.
Sarcinæ	. Groups of eight or more cocci, similarly produced.
Bacillus	. Straight rod-shaped organism.
Spirillum and vibrio	. Curved rod-shaped organism.
Spirochæta	. Flexible, corkscrew-shaped organism.
Leptothrix	. Long, unjointed thread.
Zoöglœa	. Group of agglutinated bacteria of any form.

other, as members of the Thiotrix group; and filaments like thiotrix, but destitute of sulphur-granules, as members of the Leptothrix group. In the same way filaments that branch by the lateral displacement of a cell undergoing ordinary subdivision as classified as members of the Cladothrix group (Fig. 151), and non-septate filaments, undergoing true dichotomous branching, as members of the Streptothrix group (Fig. 152). In several instances groups of organisms closely resembling one another are found to exist; examples are seen in the various acid-resisting organisms allied to the tubercle-bacillus (the grass-bacillus, the smegma-bacillus, etc.), in the group of bacteria resembling the cholera-vibrio, and in that containing the typhoid-bacillus, the colon-bacillus, and the paratyphoid bacillus. We do not at present know enough about bacteria to decide whether these are true genera and species. The streptothrix group above mentioned includes not only the actinomyces and many organisms to which the name of streptothrix is applied, but also the tubercle-bacillus and its congeners, which are found under certain conditions to develop into branching filaments.

Conditions of Life and Growth.—There is often a marked contrast between the conditions essential to the mere existence of an organism and those which are necessary for its rapid growth.

Food.—Each variety of fungus seems to differ somewhat from all others in its food-requirements, though all must be supplied with the materials whence they can obtain the elements of which they uniformly consist. These are carbon, hydrogen, nitrogen, phosphorus, sulphur, calcium, magnesium, and potassium. The first four are generally provided by carbohydrates and proteids, the rest by inorganic salts present in animal and vegetable tissues. In general terms, bacteria thrive on the complex substances present in dead and dying organic tissues, converting them into simpler compounds. Certain bacteria, however, can assimilate nitrogen and carbon from much less complex substances than albumin and carbohydrates when these are not available.

The **reaction** of the fluid has a marked influence on the growth of bacteria. As a rule, acidity is unfavorable to the development of bacteria, alkalinity favorable—the reverse usually holding for yeasts and moulds. Very slight differences may suffice to prevent the growth of a bacterium; for example, Koch was unable to produce any disease in *field-mice* with an organism which always produced fatal septicæmia in *house-mice*. Some similar difference would seem to exist between two men exposed to the poison of an infective disease, one of whom catches it, whilst the other does not. A very slight, practically imperceptible, change in the metabolism of the body or of a part may enable organisms to flourish there, even though they were quite unable to do so a short time before.

Environment.—Many **chemical substances** are inimical not only to the growth but also to the very existence of organisms. It has been

suggested that the term "antiseptic" should be reserved for those substances which *prevent* their *growth* but which do not cause their destruction; while those which *actually kill* the germs should be called "germicides." But the distinction is not an absolute one. The difference in many cases depends on the degree of concentration. Thus most germicides can be so diluted that they act only as "antiseptics," though the converse is not equally true.

Mercuric chloride is, on the whole, the most powerful chemical germicide known. A solution of 1 : 1000 will kill any spores in half an hour. Its power is increased by the addition of five times as much salt or of hydrochloric acid, while it is seriously diminished by the presence of an albuminous fluid, and absolutely destroyed by the addition of alkalies, and, therefore, of soap.

A 1 : 20 watery solution of *carbolic acid* rapidly destroys fully developed bacteria, but takes a few days to kill the more resistant spores. The addition of hydrochloric acid (half as much) increases its germicidal value. On the other hand, anthrax-spores have survived for three months at 1 : 20 of carbolic acid in *oil*, and typhoid bacilli have an unexplained tolerance for carbolic acid. Formin's aldehyde (formalin) constitutes a very powerful volatile germicide. Salicylic acid, boric acid, sulphur dioxide, chlorine, bromine, iodine, and a multitude of other substances have a weaker action.

It will be readily understood that the germicidal power of any substance must to some extent depend—(1) on the nature of the organism; (2) on the vitality of the particular specimen in question; (3) on any physical conditions that may interfere with immediate contact; and (4) on the presence of any neutralizing or incompatible substances. It must be remembered, too, that the rapidity and extent of the effect produced on organisms separated by cultivation from all the constituents of the exudations and secretions in which they are commonly found, as well as from other organisms that may usually coexist, is no *exact* measure of the effects that will be produced when wounds, cavities, surfaces of the body, or excreta are concerned. Neither must it be forgotten that the very substances which are most efficacious in destroying organisms are generally those which interfere most readily with the nutrition of the tissue-cells.

Water.—The presence of *some* water is essential to the development of all fungi, for it acts as the medium for conveying oxygen and food-substances into the cell. It is easy to add too much or too little for a given species.

Desiccation destroys some mature bacteria within a few days or hours, while others resist drying for months, and spores of the endosporous groups do so for years—it is impossible to say how long. Thus, dried cholera-spirilla die in three hours, whilst dried typhoid-bacilli survive nearly as many months, and diphtheria-bacilli longer still.

Oxygen.—Pasteur has divided fungi into two varieties—aërobic and anaërobic. The presence of oxygen is essential to the members of the first group, while it is fatal to those of the second. *Aspergillus niger*,

B. subtilis, and *Mycoderma aceti* are examples of the first group (*obligatory aërobes*); the bacilli of tetanus and of malignant œdema belong to the second (*obligatory anaërobes*). By far the larger number of pathogenic organisms are able to live either with or without oxygen—at least for a considerable time. An organism which thrives *best* in the presence of oxygen, but which *can* grow in its absence, is said to be "aërobic and capably anaërobic" (*facultative anaërobes*); and *vice versâ*. The first of these groups is the most important, and includes the bacilli of anthrax, tuberculosis, typhoid fever, and diphtheria.

Oxygen under pressure may prevent the growth of, and, after months, kill, even *aërobic* organisms. These spores, also, according to Duclaux, retain their power of germinating much longer than if oxygen is excluded; if true, this may partly explain the action of air as a disinfectant.

Temperature.—Each organism flourishes best at a particular temperature. All will grow, but less actively, at temperatures somewhat above or below this point. Now no organism can become parasitic unless the temperature at which it grows corresponds to that of some part of the body to which it finds access. *Hence it happens that all pathogenic bacteria grow readily at about the temperature of the human body.* In some cases the range within which growth is possible is very limited. Thus the tubercle-bacillus only thrives at a temperature of 99° F. (37° C.), while its growth is absolutely confined within a range of from 82° F. to 108° F. From this it may be inferred that this bacillus is less likely to exist as an external than as an internal parasite; and that, when it does affect the surface, its growth is likely to be slower and its progress more easily arrested. Other organisms, such as those of cholera and typhoid fever, can, in suitable media, grow at a temperature as low as 60° F. These can therefore easily multiply apart from the body. The general statement may be made, with regard to bacteria, that reproduction ceases when the temperature is reduced to 40° F., and in the case of many organisms at a much higher point; but they do not necessarily die. Though rendered rigid and motionless, some can survive extreme cold. The spore-bearing *B. anthracis* has been frozen in a fluid at —110° C. without injury. The maximum temperature at which bacteria can grow is in most cases between 100° F. and 120° F. By further rise of temperature, rigidity and death are induced—more easily in moist than in dry conditions, and much more easily in the adult than in the spore-form. The reaction and nature of the medium in which the germs are heated have a decided influence. Boiling, and indeed a much lower temperature (140° F.) than 212° F., will kill the great majority of fungi; but solutions containing spores may need exposure to a temperature of 212° F. for many hours before they are completely sterilized. Thus Tyndall failed to sterilize a hay-infusion by eight hours' boiling. *Fluids containing spores may be readily sterilized if boiled, for a few minutes only, on four or five successive occasions at intervals of several hours*, since the spores which can resist the heat develop in the intervals into adult organisms which are less resistant.

In like manner alternate freezing and thawing destroy organisms more rapidly than continuous freezing. Typhoid-bacilli succumb to this treatment in a month, while they resist continuous freezing more than three times as long.

Some vegetable (adult) forms have been found which withstand temperatures higher than those named. Duclaux found some bacilli (*tyrothrix* in cheese) which, when suspended in slightly alkaline fluid, were not destroyed by 100° C.; but in an acid medium were killed in a minute: the spores were not destroyed by 115° C. Other species exist, the spores of which have withstood a moist heat of even 130° C.

Streaming steam has a more powerful germicidal action than superheated steam. This is probably due to its greater degree of moisture, and its consequently greater penetrating power.

The *dry* spores of the *B. anthracis* and of the *B. subtilis* may survive nearly three hours' exposure at 140° C.

Rest.—Most fungi flourish better in a still medium than in one whose particles are constantly moving; whilst the *B. anthracis* divides actively in the blood-stream, many other kinds (*e. g.*, *Micrococcus septicus*) seem always to settle before multiplying.

Light.—Light, especially bright sunlight, has a destructive influence on organisms. The rays from the violet end of the spectrum are said to be the most powerful, those from the red end the least. All organisms do not suffer equally. Recorded experiments on this subject are contradictory. The contradiction may be due to the difficulty in excluding the influence of desiccation, oxidation, and changes in the media in which the organisms are placed. *Combined with these,* light unquestionably forms a valuable means of disinfection.

Soil.—Apart from their degree of moisture and from the presence of other organisms, the influence of most soils on the growth of pathogenic bacteria does not seem to be marked. *Peat,* however, has a distinctly destructive influence upon the organisms of cholera and typhoid fever (Dempster).

These are the principal means by which the growth of organisms can be modified. Absence of growth does not necessarily mean death of the organism. If the conditions are unfavorable the cells will not develop, but they may not die. By making a comparatively small change in some of the above conditions, the development, and consequently the action, of any given organism may be prevented. This may often be possible when it is quite out of the question to employ measures powerful enough at once to *destroy* the organisms themselves.

Distribution of Bacteria in Nature.—Earth, air, or water may be the habitat of germs: these may also exist in and on the living body.

(*a*) **Earth.**—The soil is the principal storehouse of organisms. Portions of mould taken from *the surface* and dropped into a sterilized culture-fluid invariably infect it. Pyogenic cocci and the bacilli of tetanus and malignant œdema are among the forms usually found. In

winter Koch failed to find any organisms at a depth of one metre in soil which had not been recently disturbed, which was not formed largely of decomposing material, and into which no unusual amount of water had penetrated.

All solids in contact with air, including the surfaces of animals, have organisms upon them.

(*b*) **Air.**—Spores of moulds are the commonest forms of aerial bacteria, then bacilli and their spores, whilst *putrefactive organisms are comparatively rare.* Organisms of some kind exist in the air everywhere except away from all life—in mountains above the line of perpetual snow, or on the ocean far removed from land and ships. In such places a sterilized fluid would not decompose, even if left exposed till it dried. But wherever life is found germs are found. They increase in number as the population grows and as putrescible material becomes more plentiful. Hesse found that the air in a hospital-ward in Berlin contained thirty times as many bacteria as the air out of doors. In some parts of London it is possible to pour sterilized fluids from one flask into others with the result that but a small percentage will become turbid from the growth of germs; in other parts every flask will be infected. Precautions against infection become more necessary as density of population and imperfect ventilation increase, and it is obvious that in the hospitals of large towns such measures, to be successful, must be most stringent, for here putrefactive organisms will be comparatively numerous.

The air is kept supplied with organisms from the surfaces of objects over which it passes. The dust left as the final result of putrefactive processes is a fertile source of contamination. Perfectly still air becomes pure by subsidence of its germs.

(*c*) **Water.**—All water, except such as comes from a great depth (Artesian wells), contains organisms. Rain-water sweeps the air, and infects the soil with the germs which it carries down. All surface-water is infected from the ground through which it soaks. River-water is exposed to all possible sources of pollution. It is scarcely necessary to add that, unless the water contains sufficient organic matter to serve as food for the fungi, no multiplication will take place, and that, sooner or later, the germs will die, though perhaps not for many weeks. Typhoid-bacilli in tap-water rarely survive for more than three weeks. The existence of many organisms in a sample of water points to the existence of much organic impurity, or to a continuous and plentiful supply of organisms.

(*d*) **In and On the Living Body.**—Bacteria exist in large numbers on the external (*skin*) and internal (*bronchial* and *alimentary*) surfaces, which are in contact with air. On the **skin** they are most numerous on the *hands*—beneath the nails, and in the folds of skin about the nails; and on *parts provided with hair and large glands*—*e. g.*, the scalp, axilla, and perineum. Special care is therefore required to disinfect these parts. Inhaled with the breath, organisms are found in the **larger bronchi**; but the smaller tubes and alveoli are probably free, for Tyndall has shown that the complemental air is pure, as it causes

a non-luminous gap in an electric beam thrown across a dark room. Further proof lies in the fact that empyemata communicating with the air through the lung generally remain free from putrefaction, whilst empyemata following an external wound of the pleura always putrefy.

With food and drink many living germs are carried into the **alimentary canal.** All kinds of fungi swarm in the mouth. There are fewer in the stomach, for the acid gastric juice is unfavorable to the development of most of them. They become more plentiful in the duodenum even before the food has become alkaline; and the food, when mixed with the pancreatic juice, swarms with organisms. Indeed, the products of normal pancreatic digestion and those of the ordinary putrefaction of albuminoids are practically the same. Throughout the whole intestine, but varying with the products and stages of digestion, enormous numbers of organisms occur. In abnormal states of the mucous membrane, or in too prolonged retention of intestinal contents, the fungi may multiply and excite irritation, and even poisoning, by the products of their action. Experience shows that after death putrefaction begins in the abdomen, spreading from the alimentary canal.

By obtaining pure urine directly from the urethra, Lister showed that a healthy urinary tract is free from organisms.

Bacteria on the skin and mucous surfaces may fairly be regarded as *external* to the body proper—*i. e.*, to the tissues. Virulent organisms may be found in these situations, even in healthy persons.

Organisms are found in the tissues in many diseases. There are two routes by which organisms may reach the tissues. One is *through the skin*, the other *through the mucous membranes*, especially the respiratory and the alimentary.

1. *Skin.*—As a general rule, uninjured epidermis is impervious to organisms; and in practice nearly all organisms that gain access by this means enter through wounds or slight abrasions. Pustules have, however, been produced by rubbing into the skin a pure culture of the *Staphylococcus pyogenes aureus.* Inoculation in these cases seems to have occurred through the walls of the hair-follicles or the sweat-ducts, as it does in the case of acne-pustules.

2. *Mucous Membranes.*—If organisms enter by the skin it is *à fortiori* likely that they will also enter by the mucous membranes. To decide this question so far as the respiratory tract is concerned, animals were placed in an atmosphere impregnated with anthrax-spores. In an experiment of Buchner's, out of sixty-six animals thus treated, fifty died from anthrax. It is unlikely that the organisms were swallowed and absorbed through the wall of the alimentary tract; first, because, while large numbers were found in the lungs, few or none were present in the spleen; and, secondly, because out of thirty-three animals *fed* on double the proportion of anthrax-spores only four succumbed. These experiments not only showed that in the case of anthrax the organisms can gain an entry through both these mucous membranes, but also that the entrance through the respiratory mucous membrane is the more readily effected. In the lung they are probably taken up like carbon-particles, carried to

lymphatic glands, and thence perhaps to the blood. It is difficult to deny that in many cases there may have been some slight injury at the point of entry.

Ordinarily, as above said, fresh human urine is sterile; but if animals are fed on putrid material, living organisms may be found in the urine, and in enteric fever virulent typhoid bacilli are often present in this fluid. Possibly organisms are unable to pass through healthy renal epithelium, but can escape by this channel when the cells are damaged by disease.

Experiments have been made to determine *whether organisms are habitually present in healthy tissues.* Portions of healthy organs have been removed with aseptic precautions and placed under conditions best calculated to encourage the growth of any organisms that might be present, as well as to prevent their contamination from any extraneous source. Whilst the results have been contradictory, the balance of evidence seems to be distinctly in favor of the view that, *as a rule, no living germs are to be found in healthy tissues.* That *the blood* may contain living pyogenic cocci is probable from the frequency with which inflammation and abscess result from bruises occurring in depressed states of the system (p. 284), without any break in the continuity of the epidermis. If, however, cocci could ordinarily obtain access to the tissues by means of the vessels, it would be impossible by antiseptic treatment (adapted to prevent the entry of living cocci *from without*) to prevent suppuration of wounds, for this would occur from causes reaching them *from within.*

Again, the rarity with which any collection of putrescible fluid in the body undergoes putrefaction (notwithstanding the suitability of the temperature), and the certainty with which by care we can keep wounds "sweet," seems to be strongly against the existence of *putrefactive* fungi in healthy tissues. It is certain, however, that if these do gain access they may survive for some hours; so that the putrefaction of removed portions of tissue, usually attributed to want of care, may sometimes have been due to the presence of living germs in those portions at the time of their removal from the body. Again, if a suitable nidus be provided for the development of organisms, they multiply and set up their characteristic decomposition. Thus, Chauveau performed *bistournage* of a sheep's testis—*i. e.*, subcutaneous torsion of the organ and its main vessels—in one case *before*, and in another *after*, the injection of septic bacteria *into the blood.* In the latter case, in which the testis presumably contained imprisoned organisms, it broke down into a putrid fluid, and excited much inflammation around. In the former, in which the injected bacteria were shut off from the damaged testis, the organ underwent the fatty changes previously described (p. 35). This is the invariable course when under normal conditions the operation is performed as a method of castration: it shows that, normally, organisms are not present in the sheep's testes.

Some organisms, however, seem capable of flourishing in tissues which are perfectly healthy—*e. g.*, the contagia of the acute specific

fevers, and the *B. anthracis*. Even here there is some very obscure difference between individuals of the same or of closely allied species, which renders some of them suitable media for the development of certain organisms, whilst others are unsuitable—*i. e.*, more or less predisposition is required even when a particular species is liable to a disease. Thus, some people do not appear capable of contracting the acute specific fevers: children are more subject to these diseases than adults: Algerian sheep are immune to anthrax: young dogs are easily inoculated with the *B. anthracis*, but old ones are not. One great difficulty in the experimental study of the infective diseases of man is to find animals which are subject to them. Many organisms will thrive only in some particular tissue or fluid of the body: thus, some multiply in the blood, others in lymph, others in the cerebrospinal fluid.

Conclusions.—Organisms in great variety, but in very varying number, exist in air, water, earth, and on all objects exposed to air, on the skin and on those mucous surfaces which are in contact with air. Organisms can probably pass through the pulmonary and intestinal mucous membranes in small numbers, but the majority soon die if the tissues are healthy. It is a rare thing for such bacteria to reach the urine alive. Occasionally, however, bacteria which can develop in living tissues gain entrance, and the individual invaded is then in more or less danger of disease. Organisms which can thus injure the tissues and produce diseases are termed *pathogenic*. The factors which regulate their growth in the tissues will be considered in the next section.

In the meantime it may be concluded that organisms found in a wound have entered it *from without;* that fungi found in pathological lesions within the tissues have entered by a wound or through a mucous surface; that neither living organisms nor their spores exist normally in the tissues; and that in health they are never eliminated alive by an excretory organ or by a wound.

This is of fundamental importance in surgery. If organisms could enter a wound from the side of the tissues, aseptic treatment would be impossible. As it is, we know that, if no loophole is allowed for the entry of germs from without, wounds will remain free from bacterial infection, and patients will be saved from pyæmia and septicæmia. If organisms once gain access to the tissues, it is extremely difficult to destroy the organisms without destroying the tissues as well (p. 271).

Products of Bacteria.—The chemical products which result from the growth of bacteria are numerous and diverse. To a considerable extent they vary according to the conditions under which an organism is situated; that is to say, upon the quantity and quality of the nutrient medium upon which it is living. The same organism may thus produce different substances according to alterations in its environment. For example, the cholera-vibrio, when grown in weak meat-juice, produces peptonizing ferment, but when supplied with a stronger solution forms a diastatic ferment.

Our knowledge of bacterial products is at present very limited, and

recent researches have tended rather to establish the complexity of such substances than to define their exact chemical positions. Any classification of them can, therefore, be only provisional, and is liable to alteration with every advance of knowledge in this field. The following broad ground of division may be suggested. (1) Bodies formed directly by the organisms themselves (primary products), analogous to the secretions of higher forms of life; and (2) substances which result from the action of the bacteria and their secretions upon the medium in which they live (secondary products). In the former group would fall the *ferments*, which play so important a part in the pathogenic action of micro-organisms, and perhaps, in some cases, the *pigments* with which they are colored; in the latter probably should be grouped the *albumoses*, *peptones*, *alkaloids*, *acids*, *gases*, and *pigments* produced by their activity.

In the great majority of instances the action of bacteria upon organic substances is in the direction of breaking up complex chemical bodies into simpler derivatives, as is seen in the putrefactive decomposition of dead animals and plants—brought about very largely by various species of *Proteus*—and in the fermentation of sugar, which, by various kinds of yeast (*saccharomycetes*), is converted into alcohol and carbon dioxide. Some few bacteria, on the other hand, are capable of forming more complex substances from simple materials. An example of such chemical synthesis is seen in the process of nitrification, in which ammonium salts are oxidized first to nitrites and then to nitrates by different varieties of organisms. Other bacteria found on the roots of leguminous plants have the power of forming nitrogenous compounds out of the nitrogen of the air. It is noteworthy that the products formed by micro-organisms in the course of their growth are generally, if allowed to accumulate in any quantity, poisonous to the organisms themselves, so that the growth of the latter is finally arrested in this way automatically. Thus, the yeast-fungus will not continue to grow in saccharine solutions in presence of excess of the alcohol to which it has given rise, and other organisms similarly cease to multiply in artificial media before the nutrient capacities of the latter are actually exhausted.

The toxic bodies formed by most bacteria can be extracted from the media in which the organisms have been grown. Thus, the toxines of tetanus and diphtheria exist in a very virulent form in filtered broth-cultures of these bacteria (*extra-cellular toxines*). On the other hand, in the case of the B. typhosus and the cholera-vibrio only feebly toxic substances can be extracted from such cultivations, whereas the bacteria themselves, if killed and injected into animals, are highly poisonous. It has therefore been inferred that the poisons of these latter organisms are integral parts of their body-substance (*intracellular toxines*). It is clear, however, that in order to produce toxic effects the poisons must exist outside the bodies of the organisms, and that this must be the case with living as well as with dead organisms, since it is by the living that diseases are caused. Hence the legitimate conclusion appears to be that in ordinary media these bacteria produce

little poison, but contain a certain amount in reserve within their capsules. When they enter a living host the environment is different, and the products of the bacteria differ accordingly.

The different classes of products must be separately considered.

(1) *Ferments.*—By a ferment is meant a substance of which a very small quantity is able, under certain conditions, to produce an indefinite amount of chemical change in some other body. One such condition appears to be the sufficiently rapid removal of the products of its action. In the animal economy the digestive ferments, pepsin and trypsin, are perhaps the best-known examples of this class. The action of these is very closely imitated by certain substances formed by bacteria. Thus, a ferment produced by the anthrax-bacillus is capable of forming albumoses and peptone in nutrient media, these products being very closely analogous to those formed by the gastric or pancreatic juice. The following table shows this analogy more clearly.

TABLE COMPARING ACTION OF ANTHRAX AND DIPHTHERIA FERMENTS WITH THOSE OF PEPSIN AND TRYPSIN. (MARTIN.)

Primary Agent, or Primary Infective Agent.	Ferment or Secondary Infective Agent.	Digestive Products.
Living Cell.	Pepsin.	Syntonin. Albumose { Hetero-albumose. Proto-albumose. Deutero-albumose. Peptone.
Living Cell.	Trypsin.	Globuline-like body. Tryptone (peptone). Leucin and tyrosin. A bitter body.
Bacillus anthracis.	Anthrax-ferment.	Albumose { Hetero-albumose. Proto-albumose. Deutero-albumose. Peptone. Leucin and tyrosin. Alkaloid (base).
Bacillus diphtheriæ.	Diphtheria-ferment in membrane.	Albumose { Hetero- Proto- } in the membrane. Albumose { Deutero- } Organic acid. } in the body.

The liquefaction of gelatine, so characteristic of many micro-organisms, is also due to the action of a ferment; since, if a small quantity of gelatine thus liquefied is freed from bacteria and added to a fresh tube of gelatine, the liquefying process is continued. The peptonizing power of pyogenic cocci is likewise due to a special ferment secreted by them. It is probable that the poisons formed by most pathogenic bacteria (*toxines*) fall into this group. It is impossible to

separate them in a pure state by chemical methods; they are weakened by heat or sunlight; and they require an incubation-period for their action.

(2) *Albumoses.*—It is said that the poison contained in snake-venom is an albumose, and similarly some of the poisonous products of pathogenic bacteria have been assigned to this class. Such, for example, is perhaps the case in diphtheria; but the exact nature of the poison of this disease is not certain. The active principles of the poisonous fluid obtained from cultures of tubercle-bacilli (tuberculin) are apparently albumoses. Other substances of this class, such as those formed by the organisms of cholera and anthrax, are not apparently poisonous.

(3) *Alkaloids.*—Bodies much resembling the vegetable alkaloids are formed in the growth of many kinds of bacteria, and are collectively known as *ptomaines.* Many of them are poisonous, and such are probably the toxic agents by which decomposing meat and vegetables give rise, when eaten, to symptoms of irritant poisoning (*ptomaine-poisoning*). The resemblances borne by these bodies to the alkaloids derived from plants and used as drugs or poisons causes them to be of considerable medico-legal interest, since care is necessary to distinguish, in the dead body, between substances formed in the course of putrefaction and poisons administered during life. The poison of the cholera-vibrio is probably an alkaloid.

(4) *Acids.*—The acid bodies formed by bacteria do not appear to be of much pathological importance. Instances are seen in the acetic and butyric acids formed in different varieties of fermentation. An organic acid formed by the diphtheria-bacillus possesses slight toxic properties, and one formed by the tubercle-bacillus is said to be the cause of caseation.

(5) *Gases.*—Various gases are formed in the growth of different organisms, such as hydrogen, carbon dioxide, methan and hydrogen sulphide. The property of giving rise to bubbles of gas in a solid medium, such as gelatine, is sometimes a useful test of the nature of an organism, the Bacillus coli communis, for example, being thus differentiated from the typhoid-bacillus.

(6) *Pigments.*—Many organisms in their growth give rise to different forms of pigment. This appears to be situated, in some cases, in the capsules of the bacteria. Examples of pigment are seen in the red coloration of growths of B. ruber and B. prodigiosus, the violet hue of colonies of B. violaceus, and the yellow of Sarcina flava and Staphylococcus pyogenes aureus. In most cases pigment is more readily produced at room-temperature than at body-heat. Potato is a favorite nutrient-medium for the display of colors. Pigments do not in themselves appear to be of any pathological importance. The pigment of B. pyocyaneus, which gives rise to *blue pus*, has been isolated as a body crystallizing in the form of needles, and turning red on addition of acids, like other vegetable blues.

Under the heading of pigments may be noticed the substance *indol* —a chromogen rather than a true pigment—which is of some impor-

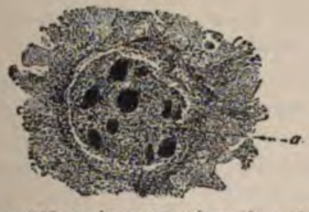
tance in the identification of certain forms of bacteria. It is one of the evil-smelling substances which normally occur in fæces, and is produced by many different organisms—the cholera-vibrio and the B. coli communis being well-known examples. The latter is distinguished from the typhoid bacillus by this property among others.

Fate of Organisms in Living Tissues.—It by no means follows that pathogenic organisms, which have actually entered the tissues, will always multiply and give rise to disease. Just as in the case of infective inflammations, so in all other infective diseases, *there are two factors in the production of disease*—the attack of the germs on the one hand, and the resistance of the tissues upon the other.

Supposing the conditions to be favorable to their growth, pathogenic fungi differ much in the course which they pursue. Some remain about the spot at which they first settled. Others, with different degrees of rapidity, spread by continuity of tissue. Others, again, are carried along in the lymphatics, settling in them here and there, or passing on until the nearest glands are reached. Another group enter the circulation at once, and are carried in the blood all over the body. Some species remain and multiply in the blood, and, in translucent parts, may be seen in the marginal stream in the veins; others, again, require to be deposited from the blood at some spot predisposed to receive them. Escape from disease after exposure to infection is doubtless often due to the deposit of germs at spots other than "weak" ones. The spread of organisms in the tissues, like that of an abscess, always occurs along the lines of least resistance.

It is not necessary that the organisms should *enter* the tissues at all in order to produce disease. In diphtheria the bacillus rarely extends beyond the false membrane; this becomes simply a factory of the ferment, which is rapidly distributed throughout the body, giving rise, in the tissues, to the albumoses already referred to. In cholera,

FIG. 153.

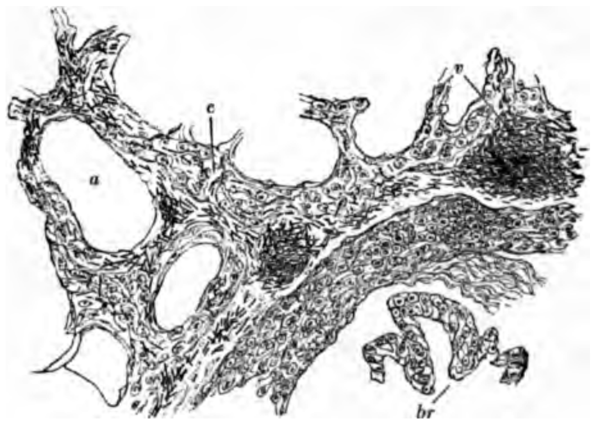


Malpighian corpuscle (*a*) from kidney in a case of septic embolism. The dark patches are "colonies" produced by the growth of pyogenic cocci arrested in the capillary tuft (*a*). The chemical products of the organisms have entirely obliterated the normal characters of the tissue, which is crowded with leucocytes. × 100.

too, the bacillus is only found in the intestine, while its products are rapidly absorbed and lead to the well-known symptoms. It is therefore clear that the effects of the action of organisms in the body are very varied. Sometimes they are strictly *local*. A small mass of organisms, by means of its chemical products, excites an inflammatory

focus and exerts a peptonizing, caustic, or other action on the tissues in which it lies (Fig. 153). The action is limited to invasion of the tissues near the point of entry. Sometimes the action is less strictly local. Such inflammation is called *diffuse*. Occasionally the mere mechanical plugging of the vessels may be of importance. The accompanying figure (Fig. 154), showing the bacillus of anthrax in the vessels

FIG. 154.



Mouse's lung: vessels plugged with bacilli anthracis. *a*, alveolus; *v*, vein full of bacilli; *c*, capillaries also full; *br*, bronchus. × 400. (Horsley.)

of a mouse's lung, gives an idea of the extent to which this process may be carried.

Sometimes, when the organisms multiply in the blood, or discharge into it the products of their action, the most marked effects are *general*. These consist mainly of fever, wasting, and coma, from the action of substances circulating in the blood, the coagulability of which is sometimes lessened. In others, again, in addition to the strictly local and general effects, the circulating products attack special parts—as in diphtheria, in which they cause marked degeneration of certain nerves, and consequent local paralyses.

Reference must here be made to the conditions which influence the two factors in question (p. 281)—increasing or diminishing the power of the organisms, or the resisting capability of the tissues.

1. **Arrest of an organism** is absolutely necessary before it can by its metabolism produce *local* irritation and inflammation, for if its products are poured into the circulating blood they become too dilute to effect any local injury. Thus, pygenic cocci have frequently been found in the blood of persons having no abscess. Again, lymphadenitis is much commoner than lymphangitis, not because the glands are more accessible to organisms than the vessels, but because the organisms are more likely to be arrested in the narrower and more sinuous channels of the former. But such arrest is not necessary for organisms which, like those of septic infection of mice, act by pouring into the blood poisons which cause fever

and other symptoms. Still, though rest is only *essential* to the multiplication of *some* organisms, it is *advantageous* to the growth of *all*.

Organisms circulating in the blood may be arrested in one of many ways. Of these the commonest are *embolism, thrombosis, extravasation of blood* from injury, and the *migration and subsequent death of a leucocyte* bearing in its interior one or more living germs :. this last will occur most easily in parts in which the vessels are distended and the circulation slow (venous congestion). It is conceivable that a germ might escape unaided from a vessel under these circumstances just as a red corpuscle does, especially when the influence of bacterial chemotaxis is borne in mind. Numerous methods have been successfully devised to cause the detention of organisms in capillaries through which they could ordinarily pass—such as mixing them with sterilized cinnabar or potato-starch. It is possible that the "clumping" of cocci *en route* may also lead to plugging of vessels, and may explain the unusual sites of many minute abscesses in pyæmia.

2. **Predisposition.**—Unless there is *predisposition* to suffer from the products of the organisms *thus arrested*, their impaction in vessels may not be sufficient to enable them to excite inflammation. Thus, in rabbits Ribbert found numerous masses of pyogenic cocci in the capillaries of the lung and other organs twenty-four hours after their injection ; but all disappeared in forty-eight to seventy-two hours except in the kidneys, where alone abscesses formed. Rabbits are less prone than man to suffer from these organisms : and in them at all events, and very likely in man also, *the resistance of the tissues must be diminished* before these particular organisms (pyogenic cocci) can excite inflammation. The resistance of the body to the attacks of organisms is diminished by **general depression of vitality.** This may arise from privation and faulty hygienic surroundings. Depressed vitality is also seen after severe attacks of acute fevers, and in alcoholic, albuminuric, and diabetic patients. Among these, trivial wounds often prove serious, and operations should, if possible, be avoided, as pyogenic cocci easily gain access, and cellulitis, boils, and carbuncles result. Among savage races and animals, serious wounds frequently heal by first intention. **Local depression of vitality** may be brought about by any kind of injury, and it is here that the "simple" causes of inflammation chiefly come in as predisponents, rendering the tissues more open to the attack of micro-organisms. It has been experimentally demonstrated that anæmia or passive hyperæmia of a part for some hours enables septic cocci to settle and excite a progressive inflammation. Thus Waterhouse injected staphylococci subcutaneously into his own scrotum with a negative result. He then constricted a portion of it, until it was purple and swollen, and made a second similar injection. An abscess resulted. The effect of comparatively slight mechanical injury in leading to simple abscess, osteomyelitis, and tubercular disease of joints has long been known, and it has been proved that such lesions act either by simply depressing the tissues or by causing extravasation of blood, and thus allowing germs which cannot grow in the circulating blood to pass out

into the connective tissue, there to multiply and excite inflammation. Ordinary chemical irritants similarly depress the tissues and excite simple inflammation, and Cheyne points out that strong injections into septic cavities probably facilitate the entry into the general circulation of any organisms which the injections fail to destroy. The injurious effect upon the tissues of great cold or heat applied directly to a part needs no comment, and Lassar's experiments (p. 184) show the effect, upon internal organs, of cold applied to the surface: and though it is not yet known how the cold acts, we may conclude that it would facilitate the passage of organisms into the tissues of the parts which become interstitially inflamed. It would seem, however, that pyogenic cocci and other organisms circulating in the blood do not enter the inflamed area and pass out into the damaged tissues *during all stages* of the inflammatory process: they do so readily until the stage of free emigration of leucocytes is reached, when—according to Rinne's experiments—they are no longer to be found in the vessels of the inflamed area. Cocci injected during the formation of scar-tissue are said to enter the vessels of the damaged parts in excessive numbers. Thence they may pass out into the tissues, but when the scar is fully formed no such difference is noticeable. The explanation given of these observations is that in the early stage of inflammation the tissues are weakened by the injury and unable to cope with invading organisms, which consequently multiply in them; but in a more advanced stage, when free escape of leucocytes is occurring, the damaged tissues are infiltrated by a swarm of healthy active cells and by an antagonistic fluid, both capable of destroying pyogenic cocci. Scar-tissue again, in its early vascular stage, seems to be of feeble resisting power. Cheyne points out that acute osteomyelitis and tubercular disease are often induced by slight injuries, rarely by severe, which seem to excite too much reaction. Improvement of the general health and the use of bactericidal serum (p. 289) may enable the tissue-elements to contend successfully against pathogenic organisms which have invaded the tissues.

3. The **seat of inoculation** and the **anatomical arrangement of a part** are of importance in enabling organisms to obtain a foothold in the body in two ways. (1) *Certain microbes* can only grow in *certain tissues;* they are harmless unless they reach and settle in these tissues. (2) The *physical characters* of a part have much to do in determining whether an organism will live in it, and what form of inflammation will result from its growth. The bacillus of malignant œdema illustrates both these points. It can grow only in connective tissue; when introduced into the blood, it sooner or later dies, leaving the animal protected against the disease; but if, whilst it is circulating, a bruise is produced, the bacilli pass out with the extravasated blood into the tissues, commence to grow and thus cause the lesions of the malady. Again, inoculation with this organism at the tip of the tail in cattle has little effect on account of the density and coldness of the part: the intensity of the inflammation increases as the point of inoculation approaches the body, and the reaction may also be increased by raising

the temperature of the more distal parts. Sheep, which have loose tissue in their tails, react strongly when inoculated even at the very tip of this appendage: the reaction is diminished by cooling the part. Cheyne showed that the injection of a certain quantity of a cultivation of the *Proteus vulgaris* into the subcutaneous tissue of the back of a rabbit caused an abscess, but the same quantity in the muscles of the back produced death; and, further, an amount of the cultivation, too small to have any appreciable effect in the subcutaneous tissue, caused an abscess when placed among the muscles. No explanation is as yet forthcoming. The limitation of acute infective osteomyelitis to growing bones is another example of the influence of structure upon disease. A last illustration of this point may be found in the difference between the behavior of the peritoneum and of connective tissue to pyogenic cocci. Washing out the peritoneum with ordinary unpurified tap-water has been practised without any deleterious effects; but the result of washing out wounds of soft parts, or of bones, has been, on the other hand, extremely unfavorable, acute inflammation often supervening. The explanation given is that the peritoneum has great powers of rapid absorption, so that even if considerable quantities of putrescible fluids be injected together with septic organisms into its cavity, they will be completely absorbed, and the organisms destroyed, before putrefaction has time to advance to a poisonous extent; but, if still larger quantities be injected, putrefaction will occur with great rapidity in the unabsorbed fluid, and death from septic intoxication will result. It is well known that a chronically inflamed peritoneum with a good many scattered adhesions stands injury better than a normal membrane, and no proof exists that the lymph-flow from the former is more free than from the latter. Possibly there are more available phagocytes in this case.

4. The **number of organisms** which gain entry to the body at any one time is a matter of great importance. At first sight, it might appear that the only difference in the results after the injection of 1 and of 1,000,000 pathogenic microbes would be the somewhat slower development of the disease in the former case. It was, however, soon found experimentally that this was not so, except in cases of animals strongly predisposed to suffer from the organism in question; and it was then understood that small numbers of organisms would be destroyed by the tissues before they could produce their products in any quantity, whilst a very large number could not be got rid of with sufficient speed to prevent them from producing more or less poison, and thus gaining a greater or less advantage over the tissues. Upon this point Cheyne's own researches enable him to enunciate the following laws. (1) The pathogenic dose of a virus varies inversely with the predisposition of the animal to the disease in question; or, in other words, the more susceptible an animal is to the disease, the smaller will be the dose of organisms required to produce it. (2) In animals not very susceptible to a germ-disease, the severity of the disease varies directly, within certain limits, with the dose: a small dose produces no effect, the germs

being rapidly destroyed; a larger one causes a local inflammation, the organisms being hemmed in and destroyed more or less speedily by leucocytes; whilst a very large dose overcomes all local limitations, the organisms penetrating into the circulation, producing poisons freely, and causing death from septic poisoning. The dose necessary to produce any one of the above results cannot be predicted with certainty, because predisposition varies greatly even among animals of the same species.

5. The **virulence of organisms**, that is, their power of self-multiplication and capacity for producing disease, may usually be increased ("exalted") or diminished ("attenuated") by suitable external conditions: thus, *attenuation* may result from cultivating an organism in such a way that long intervals elapse between the successive inoculations; or from cultivating it at a temperature at which growth is very slow, or upon media containing antiseptics in quantity not sufficient to inhibit growth. It may also be effected by passing an organism through an animal which is somewhat resistant to its pathogenic action, as in the case of small-pox; or by treating a culture with heated "immune" serum (p. 293). *Exaltation* of virulence may be produced by cultivation through a series of suitable animals, or by the simultaneous inoculation of some other bacteria or their products. Thus, attenuated diphtheria-bacilli may be rendered virulent by injecting them along with some streptococci. In the case of the spirilla of cholera it can be affected by procedures described on p. 289. As these procedures can effect such important modifications in these organisms, it is evident that the body may have to deal with them in states of varying virulence; the weaker the virus the more of it will be required to produce a given effect, and *vice versâ*. The absence of inflammation from a wound treated carelessly or left to nature may sometimes be due to the attenuation of any organisms which may have fallen upon it.

6. **Concurrent growth with other bacteria** may either increase or diminish pathogenic action, and many facts make it probable that the presence of putrefactive bacteria along with pyogenic cocci in a wound considerably increases the danger to the patient; for the putrefactive organisms, by their irritant products, destroy the granulation-tissue and open up a way of entry for the pyogenic germs. A corresponding fact, vouched for by Cheyne, is that general tuberculosis is much commoner in cases of joint-disease complicated with *septic* sinuses, than in cases which are kept aseptic. The presence of pyogenic cocci does not seem to increase the spread of tubercular cavities in the lung, but they certainly intensify the action of the B. diphtheriæ. Again, it is said that an osteomyelitis, due to a mixed infection of the Staphylococcus aureus and Staphylococcus albus, is of greater severity and of worse prognosis than a case in which only one of these species is present. The "complications" met with in many infective diseases—*e. g.*, the aural affections that occur in enteric fever, or the ulceration which occurs in the throat in scarlet fever—are probably due to secondary infection with pyogenic organisms which are able to establish themselves in tissues

weakened by the original disease. On the other hand, experiments have shown that two kinds of microbe growing in the body may successfully oppose each other. Thus, if erysipelas-cocci be injected, both under the skin and into the blood, and if a large dose of anthrax-bacilli be introduced twenty-four hours afterward, so that a large number of cocci are present in the general circulation at the time of the injection of the anthrax-bacilli, the latter will all die out in seventeen to twenty-four hours, without causing even local œdema. These two organisms will grow together readily *outside* the body, so it is not clear how their opposition *in* the body is brought about.

7. Lastly, it is probable that **local and seasonal conditions** may act upon pathogenic organisms and thus account for such peculiarities of disease as endemicity, or greater prevalence at certain times and under certain atmospheric conditions.

Immunity.—Some specific diseases tend to recur again and again in the same individual. Of these, diphtheria and pneumonia are prominent examples. Other diseases seem to show a precisely opposite tendency. To have suffered once from one of them is to have secured almost certain freedom from a second invasion. Freedom thus ensured is known as *acquired immunity*. Persons, for example, who have had smallpox are said to be immune against a second attack. It is by no means certain how long such immunity lasts; and in man there is no means of definitely ascertaining its duration. Indeed, there are good reasons for believing that pneumonia is as certainly followed by a period of immunity as is smallpox, but that the immunity lasts a much shorter time in the former disease than it does in the latter. Again, certain diseases which are common in some species of animals are practically unknown in others very closely allied to them. Thus, tuberculosis is common in pigs and cows, but excessively rare in sheep, goats, horses, and asses. Mice fall a ready prey to anthrax, while rats escape unharmed. Accordingly, pigs and cows are said to be *susceptible* to tuberculosis; while sheep, goats, horses, and asses are, on the contrary, said to be *immune* against it. The exact conditions on which this susceptibility or immunity depend are unknown. To distinguish it from the acquired form, it is known as *natural* or *inherited immunity*. When an animal is only slightly susceptible, it is often termed *refractory*. Natural immunity is rarely if ever absolute.

In human pathology there are also many examples of these peculiarities. Negroes are immune against yellow fever; white races are susceptible. A nurse in a fever hospital may never have had scarlet fever, and yet may continue to resist all exposure to the infection. It may be that inherited immunity is due to the handing down to offspring of that acquired by ancestors. Thus races, among which certain acute fevers (like measles) are common, suffer much less severely than those among whom the disease appears only at very long intervals. The complete immunity of the negro to yellow fever is gener-

ally accounted for by supposing that those who could resist the disease best would, by living longest and having most children, be most likely to hand on their peculiarities to the succeeding generation: and further, that the degree of immunity thus gained would be strengthened by the intermarriage of those already partly immune. But this explanation offers no adequate reason for the peculiar sporadic immunity enjoyed by some individuals, as in the case of the fever-nurse just cited. Occasionally, this sort of immunity is more apparent than real. Two medical students paid almost daily visits to scarlet fever wards for several months, and failed to contract the disease; but late one afternoon, on entering the wards much exhausted by severe exercise and a fast of five hours, both took the disease in a severe form, and one died.

Artificially acquired Immunity.—Just as an attack of disease may protect against subsequent infection, so artificial inoculation with pathogenic bacteria may produce immunity. Three forms of preventive inoculation have been employed to secure this result, or to arrest the development of contagia that have already reached the tissues.

1. Inoculation with attenuated organisms or with their dead bodies.
2. Inoculation with the chemical products of the organisms.
3. Inoculation with serum obtained from an animal that has been treated by one of the two preceding methods.

The first two of these comprise what is known as *active* or *direct* immunity: the third, *passive* or *indirect* immunity.

1. It has been well known since the sixth century that the artificial inoculation of smallpox produces, on the one hand, a mild form of the disease, and, on the other, confers upon its subject immunity against a second attack. In one country after another it has for a time been the custom to practise inoculation to ensure this result. It has also long been recognized that epidemics vary in severity, and that mild attacks and severe attacks are equally efficacious in securing immunity.

Pasteur was the first to place preventive inoculation on a scientific basis. He demonstrated that the virulence of some contagia can be varied by experimental procedures. In the case of chicken-cholera, he showed that by exposing cultures of the bacillus to the air for long periods its virulence became so reduced that inoculation of the weakened or *attenuated* organisms gave rise to a comparatively mild disorder, which, however, sufficed to secure immunity against subsequent attacks. Other observers have since shown that the virulence of many other organisms can also be modified (p. 286), and that the organisms can be kept in their attenuated condition through several cultivations, though there seems to be a general tendency for them to return to their previous degree of virulence. The attenuation is generally effected by one of two methods.

(*a*) A series of animals is experimentally selected, generally on account of their slight susceptibility to the disease in question. Successive inoculations are then made from one to another, until it is found that the desired degree of attenuation has been reached. (*b*) Cultures of ordinary virulence are exposed to the air, or to an increased temper-

ature only slightly below the fatal limit, or to the action of small doses of various antiseptics. Pasteur's treatment of persons bitten by rabid animals is the best known illustration of this method, though no hydrophobia-organism has yet been discovered. By a series of successive inoculations, a special virus is prepared which is known to have—when injected into rabbits—a constant incubation period of six days. Rabbits are inoculated with this virus, and their spinal cords are subsequently dried very gradually in the presence of caustic potash. The longer the drying is continued, the weaker the virus becomes. If an emulsion of a cord, that has been dried for six days, be made, and inoculated upon rabbits, it entirely fails to produce the disease. Pasteur's method is to give ten injections, extending over four days, according to the following table:

First	injection,	1st	day,	emulsion	of	cord dried	ten days.
Second	"	1st	"	"	"	"	nine "
Third	"	1st	"	"	"	"	eight "
Fourth	"	2d	"	"	"	"	seven "
Fifth	"	2d	"	"	"	"	six "
Sixth	"	2d	"	"	"	"	five "
Seventh	"	3d	"	"	"	"	four "
Eighth	"	3d	"	"	"	"	three "
Ninth	"	3d	"	"	"	"	two "
Tenth	"	4th	"	"	"	"	one day.

After three days a few more injections are given daily, and the process is complete. Statistics are strongly in favor of the efficacy of the method. There is generally plenty of time to carry it out, as the incubation-period of hydrophobia in man is never less than twelve days, and usually about six weeks. This treatment, although it is applicable after the bite of a rabid animal, is in reality prophylactic and not curative, since it fails if symptoms of the disease have actually occurred. Haffkine's vaccination against cholera affords another illustration of this method. He employs two vaccines. One is made from an attenuated virus, the other from an exalted virus. The attenuated virus is prepared by cultivating the cholera-spirilla in aërated media at a temperature of 39° C. (102.2° F.). The exalted virus is prepared in the following manner: A pure culture of the organism is introduced into the peritoneal cavity of a guinea-pig. Death follows in twenty-four hours. The peritoneal fluid is immediately removed and another guinea-pig similarly inoculated. This process is continued through a series of animals until the interval between inoculation and death falls to its lowest limit. Persons to be protected are vaccinated two or three times. On the first two occasions the attenuated virus is used; on the last, three to five days afterward, the exalted virus. The vaccination is supposed to produce a sufficient tolerance to the cholera-poison to enable the body to "react" more vigorously when attacked in the ordinary way. Sometimes the *living* cultures are used, but more often the vaccine is *sterilized* by the addition of carbolic acid. Prepared thus the fluid can be more easily preserved, and can be introduced with

less risk, but, as in other cases, the results are neither so certain nor so prolonged.

Preventive inoculation has now been tried not only in the case of small-pox, cholera, and hydrophobia, but also against enteric fever and plague in the case of man, and against anthrax and many other diseases in animals. In mankind the results are still disputed in all but small-pox, but the evidence is in favor of some measure of protection being conferred in all the cases mentioned. The immediate result of inoculation has been shown by Wright to be a fall in resistance to the disease (*negative phase*); but this passes off in the course of a few weeks, and a greater or less degree of immunity is effected.

2. In the case of those diseases in which highly toxic substances are formed in culture-media, injection of these toxines will produce immunity to the disease. Animals may thus be immunized against diphtheria and tetanus. The organisms can be *removed* by filtering fluid cultures through porcelain; or they may be killed by the action of heat, or of some volatile antiseptic, such as oil of mustard, which can be subsequently removed. Sometimes the full degree of immunity attainable is reached after two or three injections, but in other diseases and other animals the injections have to be repeated every two or three days for several weeks or even months.

3. These results led Behring in 1890 to examine the *serum* of animals thus immunized, and since that time many observers have followed in his footsteps. In the case of tetanus, the serum of immunized rabbits was used, and three very remarkable results were established. It was found that:

(1) Repeated injections of this serum will render mice, which are particularly susceptible to the disease, absolutely immune.

(2) The addition of the serum to living or to sterilized cultures of the bacillus will completely destroy the pathogenic power of each.

(3) The injection of the serum into animals already suffering from tetanus will not infrequently lead to absolute recovery.

Furthermore, it was found that, while the ordinary serum of a naturally immune animal possessed none of these properties, they could be developed by a series of similar inoculations.

This method, when applied to the treatment of disease already contracted, is known as *serum-therapeutics*, or treatment by *anti-toxin*. It is employed in tetanus and in diphtheria. The different stages comprising the whole process vary somewhat. In the case of diphtheria, the procedure adopted is, according to one method, as follows:

(1) A pure culture of the *Bacillus diphtheriæ* (Lœffler) is made in some medium giving a toxine of the greatest virulence.

(2) The organisms are removed by filtration through porcelain.

(3) The toxine thus obtained is injected into the subcutaneous tissue of a horse in small quantities, two or three times a week, until no reaction follows. Later injections are made into the jugular vein. This period extends over from one to three months.

(4) Some of the blood is then withdrawn, and the serum is separated, sterilized, and stored for subsequent use.

(5) When required for the treatment of diphtheria, a dose is injected under the skin or into a vein. Additional doses may be necessary.

The strength of the antitoxic serum is estimated by its capacity for neutralizing the toxines, so that if the two are mixed and injected together no injurious effect of any kind will result. The "immunity unit" is generally taken as one hundred times the amount required to neutralize the minimum fatal dose for a guinea-pig weighing 250 grammes. In human diphtheria a dose of 1500 to 5000 units is generally employed; but much larger amounts are not infrequently given. A much smaller dose is capable of acting as a *prophylactic* against infection.

An attempt has been made to treat tuberculosis by means of injections of the toxines formed by the B. tuberculosis, with a view to raising the resistance offered by the tissues of the patient to the growth of the organisms. Koch prepared a sterilized extract of the products of the bacillus, which was known as "tuberculin." This, when injected, produces an inflammatory reaction around the diseased foci, as a result of which the infected portions of tissue may be cast off. Up to the present time attempts to discover an antitoxine analogous to that just described in connection with diphtheria have been unsuccessful.

If animals are immunized by injecting them with the dead bodies of bacteria, or with increasing doses of living cultures, their serum acquires the property of killing and dissolving the organisms in question, but is not capable of neutralizing their toxines; in other words, it is *bactericidal, not antitoxic*. Use has been made of bactericidal serums for the treatment of disease (antityphoid, antistreptococcic); but so far the results obtained have not been very satisfactory.

Nature of Immunity.—Since bacteria, in order to produce disease, must live in the tissues and there manufacture poisons which are capable of acting injuriously upon the cells of the body, it is evident that resistance to disease may be effected in any one of three ways. The body may (1) keep out the bacteria by mechanical means, so that they cannot enter the tissues; or (2) it may destroy them as soon as they enter; or (3) it may neutralize the poisons which they produce, and thus render them innocuous. All these methods of resistance are employed in different cases.

(1) We have already seen that bacteria cannot, as a rule, pass through the healthy skin or mucous membranes, which thus constitute the first line of defence. The alimentary tract is further protected by the acidity of the gastric juice, which hinders the growth of bacteria. If they do enter by these routes, by means of slight wounds, or by the help of leucocytes which swallow them alive and then die and disgorge them within the tissues, other means of opposing them are needed.

(2) **Bacteriolysis.**—The first serious attempt to explain the me
by which destruction of bacteria within the body is brought ab
was made by Metschnikoff, who by many careful experiments ende
ored to show that the white blood-corpuscles are the agents by wh
bacteria are destroyed. Allusion has already been made to this hypo
esis (*phagocytosis*). It undoubtedly contains a large element of tru
In the case of many micro-organisms the leucocytes, assisted by c
tain chemical substances, ingest and destroy the invaders; and
other infections the leucocytes have been shown to contain within th
the substances necessary for the destruction of bacteria; but it w
shown that this destruction might occur also in blood-serum from whi

Fig. 155.[1]

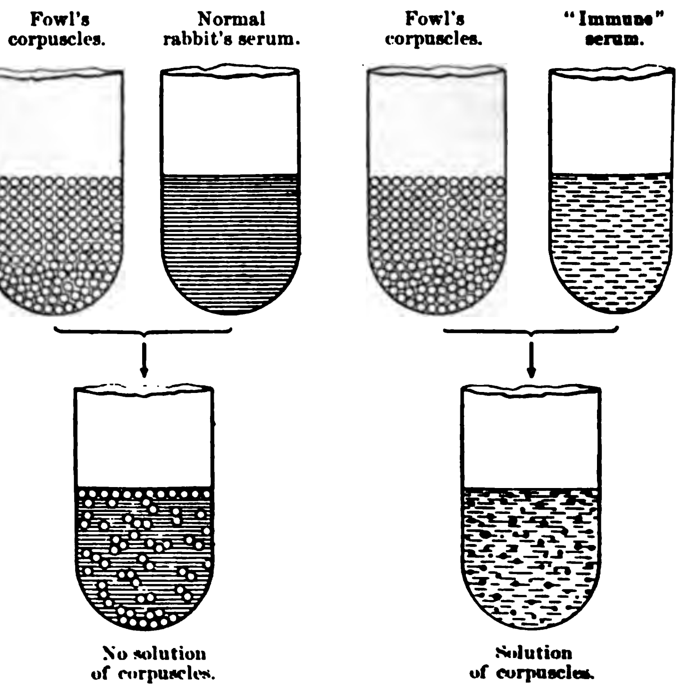


Diagram illustrating phenomena of hæmolysis.

all cellular elements had been removed, and it was thus proved th
phagocytosis does not constitute the only means of ridding the bod
of parasites. The fluids by themselves are capable of killing and di
solving many kinds of bacteria. Recent experiments have thro
light upon the complicated process by which this is effected.

It was proved experimentally that by injecting animals with sm

[1] Figs. 155 157, and 159, 160 are taken, by kind permission of Messrs. Cassel
Co., the publishers, from the present writers' book on "Serums, Vaccines, and Toxi
in Treatment and Diagnosis" (1904), in which a fuller account is given of the phenom
of immunity.

and gradually increasing quantities of a pathogenic organism, it was possible to render them resistant to considerable quantities of such a parasite. In the case of the spirilla of cholera, Pfeiffer showed that if a guinea-pig were rendered resistant to these organisms by the above means, spirilla injected into its peritoneal cavity were rapidly killed and dissolved. If some of the peritoneal fluid from such an "immunized" guinea-pig were added to a culture of cholera spirilla in a test-tube, the same process of destruction occurred. If the peritoneal exudate were heated to 68° C., it lost its bactericidal power; but if to a mixture of cholera organisms and heated peritoneal fluid a little fresh fluid from a guinea-pig which was not immune to cholera (whose peritoneal fluid was therefore by itself inert toward the germs) were added, then solution of the bacteria once more took place. By these experiments it is shown that two separate bodies take part in the destruction of the germs—one which is present in the guinea-pig before it is immunized, and which is destroyed by heat, called the *alexin;* and another which is produced in the immunized animal and which is resistant to heat, called the *copula.*[1]

FIG. 156.

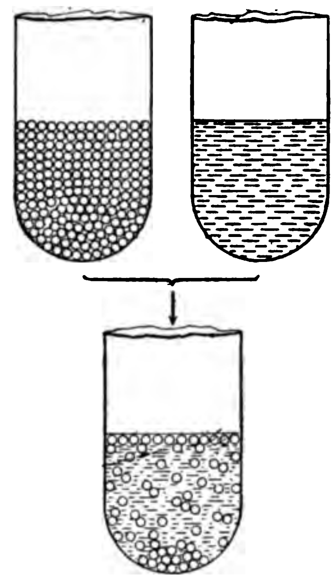


Diagram illustrating phenomena of hæmolysis.

It is not only bacteria which are destroyed by such means within the animal body: exactly the same process occurs if blood-corpuscles from one species of animal are injected into an animal of another species (*hæmolysis*), or if cells obtained by macerating the tissues of one species of animal are injected into the circulation of another (*cytolysis*). In each case destruction of the foreign material is effected by means of the interaction of two bodies, as just described. The accompanying illustrations will perhaps make the nature of the process more easily intelligible, taking the case of blood-corpuscles as the simplest (Figs. 155–157), the "immune" serum being prepared by injecting fowl's blood into a rabbit. By mentally substituting, in the above figures, bacteria or cells for the blood-corpuscles, the processes of bacteriolysis and cytolysis will be readily understood.

The complicated nature of the process of bacteriolysis may explain the comparative failure of bactericidal serums as a means of treatment. The alexin is an unstable body, and rapidly disappears from drawn

[1] Different names have been applied by different writers to each of these two bodies. Thus, the *alexin* is also known as the *complement* or *cytase;* the copula, as the *immune body, amboceptor, sensibilizing substance,* or *desmon.*

serum. If such serum from an *animal* be injected into a patient, copula remaining may be unable to unite the alexin of *human* bl to the bacteria causing the disease, and no curative effect will be p duced. Further, it is found that a single species of bacterium m contain different strains or varieties; and a serum prepared against variety is often ineffectual against another. For this reason attem have been made to prepare serums by injecting several differ strains of an organism (streptococci, typhoid bacilli) into an anim Such serums are called "polyvalent."

FIG. 157.

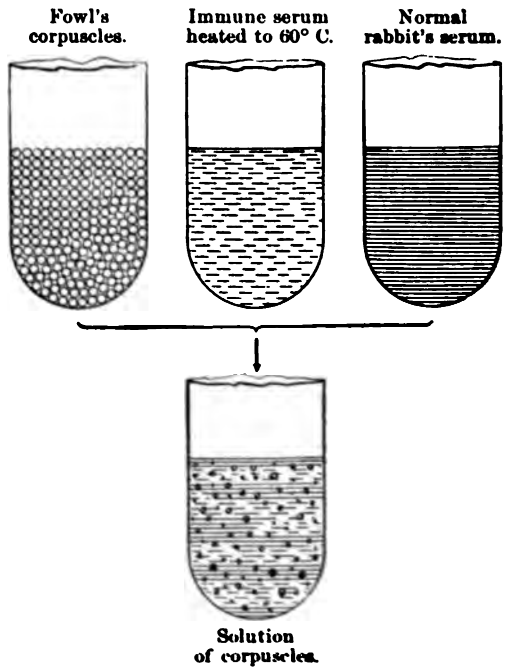


Diagram of hæmolysis.

In some cases the serum of animals immune to a particul bacterium is found not to have any bacteriolytic power; it posses instead the property of enabling the leucocytes to attack and dige the bacteria. This peculiarity is seen in the case of pneumonia an relapsing fever, and probably exists in the case of infection with ma of the common infective organisms (*staphylococci*, *B. tuberculosis*, etc. To the substances which are formed in immunized animals and th attract the leucocytes to attack the bacteria, Wright has given t name of *opsonins*.[1] The action of an opsonin appears closely resemble that of a copula.

(3) **Antitoxines.**—The third method of resistance to bacterial

[1] Greek ὀψωνέω, I furnish with provisions.

vasion is the neutralization of the toxines of the organism. If an animal is injected with gradually increasing doses of the toxines of a pathogenic organism, it is found that not only does it become immune to that organism, but that its serum is capable of neutralizing the toxines of the bacterium if added to them in a test-tube; so that the mixture is no longer harmful to other animals if injected into them. Further, the "immune" serum is capable of cutting short an attack of the disease already induced in a non-immune animal. It is thus proved that the serum of an animal immunized against the toxines of a particular organism contains a body capable of directly neutralizing the toxines of the organism, not only within the system of the immunized animal, but also outside it. This body is called an *antitoxine.* With regard to the interaction of toxine and antitoxine many curious facts have been ascertained. In the first place these bodies combine to neutralize one another in exact quantities, like an acid and an alkali; but the resulting mixture can be again separated into its component parts by filtration through a porcelain cylinder, the toxine passing through, while the antitoxine remain. Again, it is possible to make a mixture of toxine and antitoxine which shall be innocuous to one species of animal, but toxic to another. Further, if a mixture of toxine and antitoxine be injected into a living animal, the toxine may appear uncombined in the urine. It would seem that the combination between toxine and antitoxine is loose and readily dissolved; and also that the combination takes place slowly. If toxine and antitoxine are left long in contact, the above peculiar phenomena no longer occur.

In the case of the toxines of diphtheria it is found, by gradually adding more and more antitoxine to the poison and injecting the mixtures into animals, that there are present in the crude poison of the bacterial culture several different bodies of varying toxicity, possessing different degrees of affinity for the antitoxine; one of these, called *toxoid,* or prototoxoid, is practically inert, but has the greatest avidity for antitoxine; a second (*toxone*) has little affinity for antitoxine, and is apparently responsible for the production of the local œdema which occurs in the tissues at the site of injection of diphtherial organisms or toxines; while the most toxic body, to which the main effects of the disease are due, occupies an intermediate position with respect to its affinity for antitoxine.

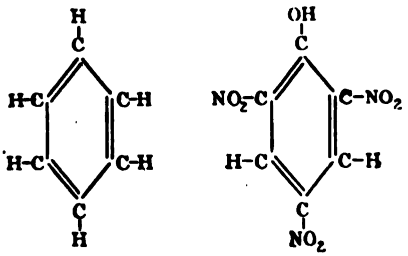
The serum of an animal which has been injected with the toxines of an organism does not possess any destructive (bactericidal) power toward that organism. Thus, diphtheria-bacilli will grow freely in diphtherial antitoxic serum. An injection of such antitoxine does not kill the bacilli present in a patient, but it prevents their further growth in the tissues, which is effected by means of the action of the toxine.

Ehrlich's Theory of Immunity.—In organic chemistry many complex substances seem to possess a central group of molecules which remains stable throughout a series of combinations and resolutions, and outlying groups of molecules which enter into combination with other radicals. For example, the benzene ring remains as a recogni-

zable centre of attraction throughout a series of compounds, of which trinitro-benzene may serve as an example (Fig. 158). In all of these there is a constant centre of attraction, consisting of the six linked atoms of carbon, which grapple to themselves other groups of atoms.

Ehrlich supposes that the animal cell consists of a central mass of protoplasm corresponding with the benzene ring; and that to this are united a series of outlying groups of molecules, or "side-chains," which have the power of entering into combination with substances circulating in the lymph around the cell. These outlying groups are called *receptors*. Under ordinary circumstances their function is to take up molecules of food for the nutrition of the cell; but they are also capable of uniting with other substances which may act harmfully instead of beneficially. Taking the instance of hæmolysis as illustrated in the foregoing diagrams, the cells, or rather corpuscles in question are not fitted for entering directly into combination with the destructive body or alexine existing in the blood of the animal into which they are injected; but this combination can be brought

FIG. 158.



Benzene. Trinitro-benzene.

Chemical formulæ of benzene and trinitro-benzene, showing central ring and side-chains.

FIG. 159.

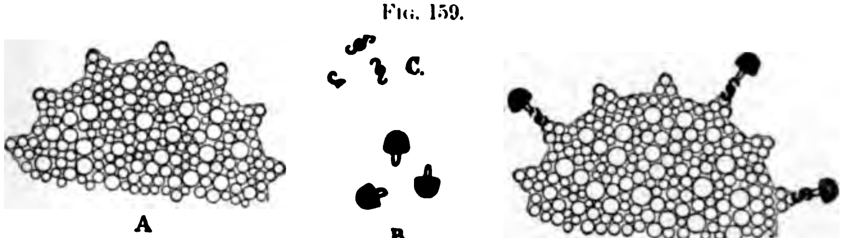


Diagram illustrating action of alexin and copula · *A*, cell or corpuscle with side-chains or receptors; *B*, alexin; *C*, copula · *D*, cell with alexin united by copula to its receptors.

by means of a second body, formed in the immunized animal, which acts as intermediary and grapples corpuscles and alexin together. (See Fig. 159.)

When a cell is brought into contact with a bacterial toxine, a similar process takes place, only here no intermediary body is necessary, as the toxine contains within itself distinct groups of molecules corresponding with both the alexin and the copula. These groups have been named the "toxophore" and the "haptophore" respectively (Fig. 160). If a small quantity of toxine combines with the receptors of a cell, it is capable of killing some of these receptors, but the cell itself escapes. The cell then proceeds to throw out more of

the receptors which have been killed; and, as is not unusual in the process of repair of injury, the new receptors are formed in excess of the original number. The cell thus becomes provided with a greater number of side-chains capable of entering into combination with the toxine in question, and is thus able to tolerate larger and larger doses of the poison. As this process goes on, so many of the receptors are formed that some of them are cast off into the lymph and enter the blood-stream (Fig. 160). *These free receptors are the antitoxine.* They are able to unite with the molecules of toxine before these reach the cells, and thus to neutralize them. They can also be injected into the body of another individual, and will fulfil the same function there, protecting the person or animal injected against subsequent doses of poison. If the toxine exists in the blood of the person injected before the antitoxine is administered, this will still be capable of neutralizing any part of it which is still free and uncombined with the cells. It would seem that it is even able to withdraw some portion of the poison which has already combined with the receptors of the cells so long as

FIG. 160.

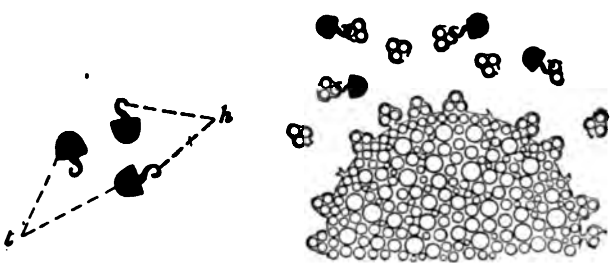


Diagram illustrating formation and action of antitoxin. *A*, cell with receptors increased in number; some of these have been cast off into the circulation and are uniting with molecules of toxine; *B*, toxine, showing (*h*) haptophore and (*t*) toxophore groups.

this combination has not become too firm—*i. e.*, probably before the toxine has not only united with the receptors of the cells, but has also gone further and entered into combination with the central protoplasmic mass. When this last has once taken place, no amount of antitoxine can be of any avail. Dönitz ascertained the exact amount of diphtherial antitoxine which would neutralize a given dose of toxine in a test-tube, and found that the same quantity was capable of protecting an animal against injurious effects if it were injected within nine minutes after the administration of the corresponding amount of toxine. If a longer time elapsed, it was necessary to give considerably more antitoxine to protect the animal; while if more than two hours had elapsed between the injection of the toxine and the administration of the antidote, then no amount of the latter would avert a fatal issue: the toxine had become so firmly united to the cells that no quantity of antitoxine would withdraw it.

Immunity to an infection may thus depend on any of the following **conditions**: (1) The tissue-cells may possess no receptors capable of

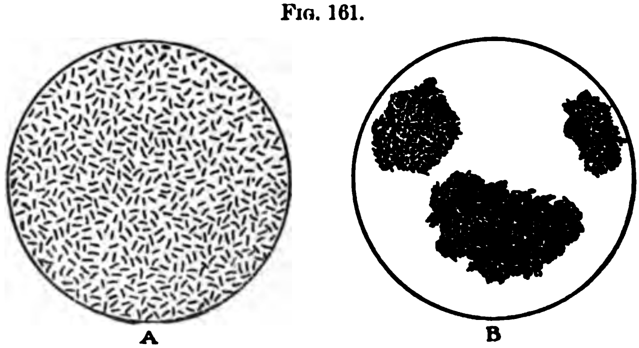
uniting with the toxine in question: thus, the toxine of tetanus can be injected into the tortoise without producing any poisonous effect, but if the blood of the animal thus treated is injected into a mouse, the latter dies of tetanus. This shows that the toxine exists free in the blood of the tortoise, having no power of entering into combination with the receptors of this animal. (2) The serum may contain antitoxine, either naturally existing there, or formed in response to repeated injections of small quantities of toxine, or to a by-gone attack of the disease caused by the organism; or owing to the injection of some antitoxic serum from another animal which has been thus immunized. (3) The serum of the animal or person may be bactericidal, possessing in it the bodies, alexin, and copula necessary for destroying the bacteria which cause the disease, or those substances which enable the leucocytes to attack and digest them.

The passive immunity gained by injection with the serum of another immunized animal only lasts for a short time; the antitoxine or the copula, in the case respectively of antitoxic and bactericidal serum, being either excreted, or neutralized by the formation of antitoxine or anticopula.

The origin of the copula or immune body is not known; it possibly represents a special kind of receptor formed by the cells. The alexin is probably formed by the leucocytes in many cases; in some instances it, too, may be produced by the tissue cells. In exhausting diseases the supply of alexine present in the blood falls to a low ebb, and the attack of parasitic organisms is thus facilitated (*terminal infections*). It is in the same way probably that starvation and overwork diminish resistance to disease.

The serum of persons who have suffered from an infective disease, and that of animals which have been experimentally inoculated with bacteria, exhibits certain other special properties in addition to bacteriolytic and antitoxic powers: these may be briefly considered here.

FIG. 161.



A B

Diagram illustrating the agglutination of B. typhosus by serum from a typhoid-patient.

Agglutination.—The blood-serum of patients suffering or convalescent from enteric fever was found by Gruber and Durham to have the

power of causing the bacilli of the disease to adhere together in clumps instead of moving freely about, as they normally do (Fig. 161). The same property is exhibited by the serum in other diseases toward the bacteria responsible for the infections (Malta fever, dysentery, etc.). This power of agglutinating the bacteria persists even when the serum is considerably diluted. Undiluted serum from a normal person has some agglutinating power, which is also exhibited by some chemical agents, such as perchloride of mercury.

Use has been made of the property of agglutination as an aid in the diagnosis of disease. For practical purposes the reaction may be obtained in either of two ways: (1) By adding diluted serum in measured quantity to a known amount of a freshly made culture of the bacilli, and observing a hanging-drop of the mixture under the microscope; or (2) by adding the diluted serum bulk to a suspension of the bacteria in a test-tube, in which case the liquid becomes gradually clear, the bacilli settling to the bottom as a precipitate (*sedimentation*).

If a small proportion of the serum of an immune animal be added to a culture of bacteria, and the growth of these watched under the microscope, it may be seen in some cases that the growth takes a peculiar form, the organisms tending to form long chains or to be otherwise altered in appearance (pneumococcus, etc.).

The nature of the process of agglutination is not known. It is possible that a precipitate of some kind is formed, which entangles the organisms in its meshes. The substances which produce the reaction are called *agglutinins:* there is evidence to show that the interaction of two bodies analogous to the alexin and copula which produce hæmolysis is necessary for the process of agglutination.

The hæmolytic serum of animals injected with blood from other species acquires the power of agglutinating the corpuscles of this species as well as dissolving them.

Precipitation.—If the serum of one species of animal be injected into an animal of a second species, the serum of the latter gains the power of producing a precipitate when added to the serum of any individual of the former species. Thus, if the serum of a man be injected into a rabbit, the serum of this rabbit will produce a precipitate with any human serum. This reaction is not absolutely "specific," inasmuch as serum from closely allied species may be influenced in the same way as that of the animal employed for the injections: thus, in the above instance the serum of apes will be precipitated as well as human serum—an interesting confirmation of the true biological relationship between man and the anthropoids. The serum of the actual species used for injection will, however, give the reaction in considerably greater dilution than that of the allied forms. It has been suggested that use should be made of this reaction for medico-legal purposes, when it is desired to identify blood-stains as being of human origin. The substances which are produced in the injected animal and which induce this reaction are called *precipitins.*

Methods of Investigation.—1. Recognition of Micro-organisms.— The large majority of bacteria are so small that special staining is necessary in order to display their form and general characters. Bacteria (like nuclear chromatin) stain readily with basic aniline dyes, but often retain the stain under conditions that will decolorize animal tissues. The dyes most often used are fuchsine, methyl violet, methylene blue, and, for photographs especially, Bismarck brown: freshly filtered watery solutions are employed, from 0.5 to 5 per cent. Cover-glasses and slides should be cleaned with chromic, or with dilute nitric, acid and kept in absolute alcohol; before use they should be heated in a spirit-flame whilst held in forceps. The following is the method of procedure in the case of **fluids**. A small drop of the material to be examined is taken up in the end of a sterilized platinum loop and smeared evenly over one side of a clean cover-glass. This is preferable to the older method of squeezing the material between two cover-glasses and then sliding them apart. The cover-glass is next set aside, film-surface obliquely downward, to dry, and then passed three times through a Bunsen-flame, at a rate of one foot per second, to precipitate and fix any albuminous material to the glass. If a weak staining solution is used, the cover-glass must be floated on it, prepared face downward, for some minutes or hours: if a strong solution (2 to 5 per cent.) is employed, a few drops may be poured on to the dried cover-glass and left for half a minute. In either case the cover-glass is then washed with distilled water from a wash-bottle, dried over a flame, and mounted with Canada balsam dissolved in xylol.

It is sometimes desirable to stain the bacteria one color and the rest of the specimen another. This may be done by first of all staining the cell-protoplasm with eosin, and afterward the nuclei of the cells and the bacteria with methylene blue or some other contrast-stain. If, however, some special means be taken to fix the dye in the bacteria, as by the use of aniline oil, carbolic acid, alkalies, heat, or prolonged staining, it is possible to stain some organisms so that they will retain the dye, even when they are acted on by a solution of nitric acid (1 in 5), which decolorizes everything else, including other kinds of bacteria. After the acid has been washed off, the decolorized parts may be stained with some contrast-color—*e. g.*, vesuvin or methylene blue. The chief pathogenic fungi known to stain in this way are the bacilli of tuberculosis and of leprosy. The bacilli of tuberculosis are now constantly sought for in pus, in sputum, and in urine, either for purposes of diagnosis, or to learn the result of treatment. For the examination of fluids for this organism the Ziehl-Neelsen stain is generally employed. After staining in the warm fluid for some minutes, the films are decolorized with a 20 per cent. solution of nitric acid, washed in alcohol, then in water, and subsequently counterstained with a solution of methylene blue (half a minute) or Bismarck brown (three minutes), and finally washed, dried and mounted.

A method of very general use in the search for bacteria was introduced by Gram of Copenhagen. Prepared cover-glasses are soaked

for some minutes, and sections for some hours, in Ehrlich's solution of gentian violet,* until they are deeply stained. They are then placed on or in a solution of iodine † until they turn brown (*i. e.*, two or three minutes). The specimens are next decolorized in alcohol, counter-stained, if necessary, with eosin or Bismarck brown, dried and finally mounted in Canada balsam. Some organisms remain deeply stained, but some—such as the gonococcus and Friedländer's pneumo-bacillus—are decolorized. This method of staining often helps to distinguish allied forms of bacteria.

When tissues are to be examined, small pieces should be placed, as soon as possible after death, in strong methylated spirit or in absolute alcohol. When thoroughly hardened, sections should be cut in paraffin, as they must be very thin. The sections are stained for twelve hours or longer in a 1 per cent. freshly filtered watery solution of the dye selected, or for a shorter time in a stronger solution (warmed). Some workers next transfer the stained section to a 1 per cent. solution of glacial acetic acid, then to absolute alcohol, and finally to whatever clarifying agent is employed (cedar oil, xylol, coal-tar naphtha) : others, omit the acetic acid. Each of these fluids dissolves some of the dye out of the tissue, and the difficulty is to reduce this effect to a minimum. It is best, therefore, at first to take only one section at a time out of the staining fluid. One or two trials will show how long the section must be left in each fluid in order that it may finally retain a rather pale color. The specimen is then mounted in Canada balsam dissolved in xylol.

If a blue or violet stain has been used, the sections, after washing in alcohol, may be dipped in water for a moment, and then placed in eosin- or carmine-solution for an hour; the tissue-elements acquire a red tint, whilst the organisms remain blue or violet. The sections must now be placed in alcohol. The subsequent stages are the same as before.

To examine tissues for B. tuberculosis or B. lepræ, the Ziehl-Neelsen stain‡ is the best. Place the sections in the fuchsine solution, and leave them in a warm place for at least two hours; then transfer them to the nitric acid solution and leave them until the color is almost gone; then rinse them in water and put them into methylene blue for an hour. Next pass them through absolute alcohol and whatever clearing reagent is used, and then mount as before. B. tuberculosis and B. lepræ will appear as red rods on a blue ground; all other organisms present will be blue.

With loose sections it is a good plan to use the glass slide as a section-lifter, pushing it obliquely into the xylol or the alcohol, and there spreading the section out upon it. Large vessels and plenty of the fluid must be used for this purpose.

* Saturated alcoholic solution of gentian violet, 5 c.c. ; aniline water, 100 c.c.

† Iodine, 1 grm. ; potassium iodide, 2 grm. ; water, 300 c.c.

‡ Dissolve one gramme of fuchsine in 10 c. c. of alcohol, and add 100 c. c. of a watery solution of carbolic acid (1 in 20).

With large organisms, or with successful contrast-staining, a magnifying power of 500 diameters and ordinary illumination will be sufficient for most clinical purposes; but for the smaller fungi and for accurate observation an oil-immersion lens, and a sub-stage condenser of very wide angular aperture, are necessary.

II. Cultivation of Micro-organisms.—When the presence of organisms in a fluid or tissue has been determined, it may be necessary to cultivate them, in order either to study their life-conditions or to separate them from all other species and other matter. Cultivations may be made in fluids or on solids, previously sterilized, in order to ensure the absence of any living organisms other than those purposely introduced.

Heat is invariably employed as the sterilizing agent, as chemical germicides cannot be removed, and their continued presence vitiates the results.

Moist heat is the most useful agent. Instruments, boiled for ten minutes, are, under ordinary circumstances, efficiently sterilized; though, if spores be present, boiling for an hour is essential. This method is especially suitable for steel instruments, as they are injured less by moist than by dry heat. Steaming at a temperature of 100° C. practically fulfils the same purpose as boiling, though continuous steaming for an hour and a half is necessary to destroy spores. Equally good results can be obtained by steaming for a quarter of an hour on each of three successive days. To shorten the procedure as far as possible, sterilization is often effected by steaming under pressure, which is increased so that the water will not boil until a temperature of 115° C. is reached. Steaming under these circumstances will effectually sterilize in a quarter of an hour. Many media are, however, damaged by any of the preceding methods—*e. g.*, blood-serum, which coagulates at 60° C. To sterilize media without damaging them by heat, it is customary to subject them to a temperature of 57° C. or 58° C. for one hour on each of four consecutive days.

Dry heat, although less efficacious than the same degree of moist heat, is used for two purposes. (1) Platinum needles and cover-glasses may be sterilized by being passed through a Bunsen-flame and heated to a dull red. (2) Apparatus, especially when made of glass, can be sterilized in a temperature of 160° C. to 180° C. In this way the apparatus is kept dry and ready for immediate use. To avoid fracture the temperature must be gradually raised and gradually lowered.

Culture-media may be fluid or solid. *Fluid media* were the first employed. To sterilized broth or other fluid containing some material likely to afford nutriment for the organisms under investigation, a small quantity of the substance suspected to contain them was added. Under suitable conditions the organisms grew, and the fluid became turbid. A small quantity of this culture-fluid was then placed in another flask containing a similar medium, and so on until the culture was freed from all material incapable of growth. If more than one kind of fungus is inoculated in the first instance, it may be impossible by this means to ensure a pure cultivation of any of the original organisms.

Koch introduced transparent *solid culture-media*. To clear meat-broths peptone is added, and the mixture stiffened by the addition of sufficient gelatine (5 to 10 per cent.) to render it solid at 65° to 80° F., at which temperature most fungi will grow fairly. Agar-agar, obtained from dried seaweed, is now used (1 to 2 per cent.) to stiffen fluids required to remain solid at temperatures above that of the melting-point of gelatine, in order that the life-conditions of organisms at any temperature possible in the body may be determined. Solidified blood-serum, potatoes, milk, and other media are also employed. The employment of solid media was a great advance in practical bacteriology, as it enabled investigators, by cultivation, to free one species from all other species and other matter, as well as to observe any distinctive characters assumed by organisms growing on special media, and to ascertain the conditions and products of growth of bacteria in substances resembling as closely as possible the animal tissues in which the bacteria are known to thrive. It will be readily understood that for these purposes a very large number of different media are required. Media in a fluid state are still necessary for the inoculation of animals, for the separation of the products of bacteria by filtration, and for experiments on the germicidal influence of different chemicals. In all cases the nutrient-media must be carefully sterilized; and in inoculating a culture-tube great care must be taken to prevent contamination from the air or apparatus.

Transparent solid media are generally employed in one of two ways.

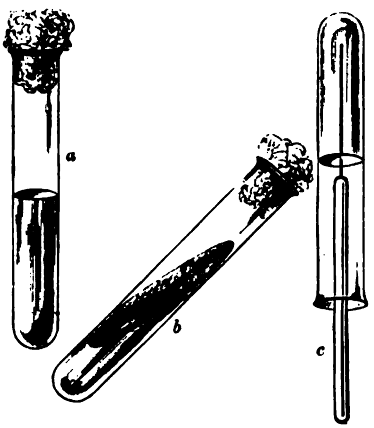
α. **Tube-cultures.**—Fill the lower third of a test-tube with the selected culture-medium; insert a plug of cotton-wool into the orifice of the tube; sterilize according to the method just described, and then set the tube aside to cool, either in a vertical or an oblique position, according to whether depth or surface is required. This and the following details are shown in Fig. 162. To make a cultivation on the medium thus prepared remove the plug from one of the tubes, then with a sterilized platinum wire take some of the suspected material and transfer it to the culture-ground, stabbing or smearing this with the wire (Fig. 162). Re-insert the plug, and put the tube—the right way up—in an incubating chamber under such conditions of temperature as may be desired.

Colonies of organisms will gradually appear (1) on the surface only, if oxygen is essential (*aërobic*); (2) in the lower part of the track only, if oxygen is fatal (*anaërobic*); or (3) on the surface and along the track, if the presence of oxygen is a matter of comparative indifference. In some cases the form of the growth is characteristic (Fig. 164); in others the media are liquefied in some peculiar and, therefore, diagnostic manner (Fig. 163).

β. **Plate-cultures.**—Warm the medium until it is just fluid, and inoculate a tube as before, but without inversion; gently agitate the contents, inoculate a second tube from the first, and then a third from the second. Pour the contents of each on to separate glass dishes, and keep these in glass-covered chambers under the desired conditions.

Isolated colonies will gradually develop in different proportions on each plate, and, if very numerous, may run together. Different organisms will produce colonies differing in appearance. Tubes can be subse-

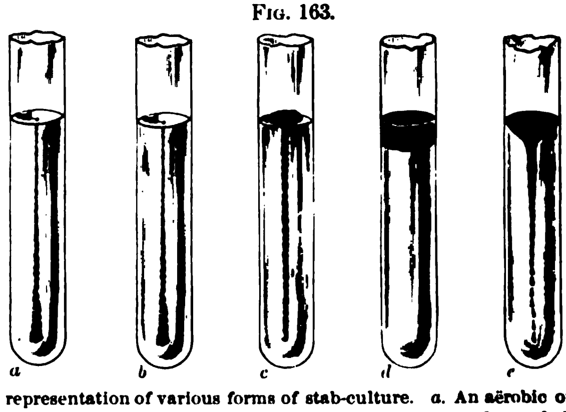
FIG. 162.



Culture tubes. *a.* Tube prepared for "stab" culture; *b.* Tube prepared for "streak" or "smear" culture; *c.* Method of making "stab" culture. It is now customary not to invert the tube.

quently inoculated from any of these colonies which it is desired to isolate. Thus, for each organism we can ascertain the influence of different temperatures, media, and gases, as well as separate one

FIG. 163.



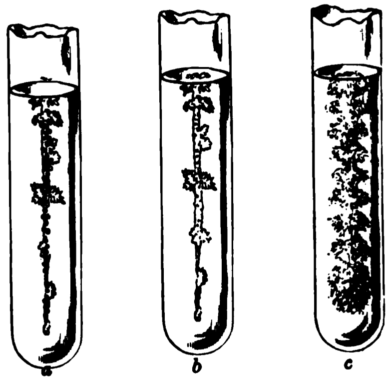
Diagrammatic representation of various forms of stab-culture. *a.* An aërobic organism—grows therefore only on surface: *b.* An anaërobic organism—grows therefore only beneath the surface; *c.* An organism indifferent to the presence of air—grows therefore on and beneath surface; *d.* An aërobic organism which liquefies gelatine; *e.* An aërobic but capably anaërobic organism, which also liquefies gelatine, but in a different manner to *d.*

organism from any others that may have been simultaneously introduced.

To examine air, a glass plate covered with gelatine-peptone may be

exposed for a given time, and then kept under a moist bell-jar: colonies will grow wherever germs have fallen, and any of them can be subsequently cultivated in tubes. Again, a portion of earth or tissue may

FIG. 164.



Tube-cultures, showing peculiarities of growths along the lines of puncture. (After Sternberg.)

be broken up in sterilized water, and a little of this may be shaken with sterilized peptone-gelatine; the latter is then poured on a plate and allowed to set. Most frequently such cultivations are carried on in test-tubes, inoculated with a platinum wire heated to redness and allowed to cool just before it is dipped into the substance to be examined. A puncture with it is then made into gelatine. A very handy method of cultivation is the inoculation of slices of recently boiled potato, cut with a sterilized knife, and kept under a bell-jar in moist air.

In all experiments the apparatus must be carefully sterilized, and each procedure carried on in as still and pure an atmosphere as possible.

Pathogenic Bacteria.

A more detailed reference will now be made to those bacteria which, on more or less satisfactory evidence, are believed to be the exciting causes of certain infective diseases. For want of a better classification we shall divide them into three groups—*micrococci*, *bacilli*, and *spirilla*.

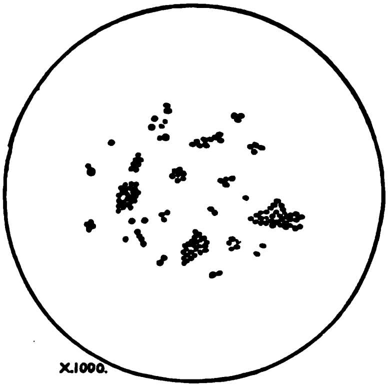
I. Micrococci.—These are round or oval cells, generally 0.5 μ to 2 μ in diameter. They are arranged (1) singly, (2) in pairs (*diplococci*), (3) in chains (*streptococci*) of four cocci to three hundred, which may be straight or wavy, (4) in groups like bunches of grapes (*staphylococci*), or (5) in colonies and zoöglœa-masses. The organisms belonging to this order differ among themselves in form, size, mode of grouping, and physiological action.

The absence of distinctive form makes it very difficult to ascertain whether a culture is "pure," and whether a coccus under observation is the cause of any given disease. Of all forms of fungus, cocci are the most frequently associated with disease.

1. Fermentation of Urine.—The *Micrococcus ureæ* causes ammoniacal fermentation of urine, by forming ammonium carbonate out of urea and water. It is generally deposited from the air. Urine obtained pure, and exposed only to pure air, will keep acid for years. The transformation of urea into ammonium carbonate is due to the action of a so-called *intracellular ferment* in this micrococcus (p. 278). The nature of the ferment is shown by the facts (1) that if the cocci be removed by filtration the change ceases, and (2) that a body capable of producing the change can be extracted from the cocci by the action of alcohol. If cocci be accidentally introduced by means of instruments the change may occur in urine contained in the living bladder, and may extend up to the pelvis of the kidneys with the most fatal results (see Suppurative Nephritis). The M. ureæ is rather large (2 μ), and occurs singly or in chains.

2. Suppuration, or pyosis, whether in the form of acute abscess (p. 170), osteomyelitis, or metastatic pyæmia, is usually due to the

FIG. 165.



Staphylococcus pyogenes aureus. From a culture. × 1000.

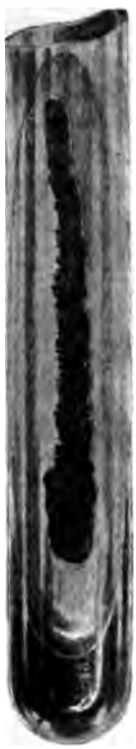
FIG. 166.

Streptococcus pyogenes. From pus found in a pyæmic abscess. × 1000.

presence of cocci. Many varieties of cocci possess the power of producing pus. By far the most common of these are the *Staphylococcus pyogenes aureus* (Fig. 165), the *Staphylococcus pyogenes albus*, and the *Streptococcus pyogenes* (Fig. 166). They all grow readily at the temperature of the body. The *Staphylococcus pyogenes aureus* and the *Staphylococcus pyogenes albus* differ from one another in only one important particular; namely, that the former, when cultivated on gelatine, agar-agar, or potato, in the presence of oxygen, produces a pale orange pigment, while the latter does not (Fig. 167). They resemble one another in forming clusters, in liquefying gelatine, and in being able to exist for weeks in the dry state. Moreover, when introduced into the tissues under favorable circumstances they both form a peptonizing ferment: albumoses and peptones can always be obtained from pus. The *Streptococcus pyogenes* consists of cocci rather larger than

the preceding, and grows in chains. It does not liquefy gelatine, and does not form pigment (Fig. 168). When introduced into the tissues

FIG. 167.



Staphylococcus pyogenes aureus. Streak-culture on nutrient agar-agar.

FIG. 168.

Streptococcus pyogenes. Streak-culture on nutrient gelatine.

its effects vary with its virulence. Sometimes it produces erysipelas, sometimes abscess, sometimes septicæmia. The staphylococcus is principally found in circumscribed abscesses, while the streptococcus is especially associated with spreading and diffuse suppuration.

All these organisms exist in considerable numbers on the skin, especially where they can "obtain cover." They reach wounds by growing under the dressings, and not, as a rule, by falling from the air. Minute quantities of boric acid (1 : 300, applied to cultures) and other antiseptics suffice *to stop their growth*. Observers are by no means agreed as to the length of time which a 1 : 1000 solution of mercuric chloride takes to *kill* them, the times given varying from eight seconds to thirty minutes. Possibly these divergent results depend on the different virulence of the specimens tested, and may be said to be consistent with the results obtained by inoculation.

In the case of these organisms the chain of proof demanded (p. 264) is almost complete. Ogston inoculated eggs with cocci from an acute abscess. By a series of cultivations he obtained the cocci "pure," and with these he successfully inoculated animals. Although abscesses were the usual results, well-marked septicæmia occurred in some cases. Cocci were then found in the blood, though never in very large numbers.

Further proof that these organisms can cause suppuration has been given. Similar operations were performed with antiseptic precautions on both eyes of each of a series of rabbits, and one eye in each animal was inoculated with pyogenic cocci, chiefly the *Staphylococcus pyogenes aureus:* all the aseptic eyes healed without suppuration, while all those infected suppurated and were destroyed, except some in which the operation was quite superficial (Knapp). Upon man numerous experiments have been made: cultivations of staphylococci have been inoculated upon the cutis and have led to the formation of small abscesses. Similar cultivations have been rubbed into the normal skin of the arm and have induced the formation of numerous impetiginous pustules. Boils and, in one case, a large carbuncle have been produced in a similar manner. Lastly, the subcutaneous injection of these organisms has resulted in the formation of abscesses (p. 283).

Under ordinary circumstances pyogenic cocci can enter the skin by the orifices of ducts or through small abrasions. *Impetigo* results, if they gain entrance to the ducts and multiply there without penetrating the true skin. If the cocci reach the depths of a hair-follicle or sweat-gland their action is more violent, and they produce a slough —*a boil* results. When the cocci actually penetrate the cutis vera they cause an abscess of the skin.

In **metastatic pyæmia** the proof is not quite so complete. Large numbers of micrococci are found in the secondary foci. It has, moreover, been shown that the unhealthiness of a wound is in proportion to the number of zoöglœa-masses on its surface, and the severity of the disease to the number of cocci in the blood; whilst the cocci have been traced from the wound into connective-tissue spaces and even into a vein. They are present in all clots undergoing infective softening. On the other hand, large numbers of cocci have been found in the blood of healthy persons.

Concerning the special organism present, it may be noted that Rosenbach examined six cases of metastatic pyæmia and found the *Streptococcus pyogenes* in five, in two of which it was accompanied by a smaller number of *Staphylococcus pyogenes aureus*. In one case—the only one which recovered—the latter coccus occurred alone.

In **acute suppurative periostitis** and **osteomyelitis**, Rosenbach demonstrated that the *Staphylococcus p. aureus* was present in the great majority of cases; and he was further able to support Lœffler in his statement that the same organism, when injected into the veins of animals whose bones had been bruised or fractured, caused acute osteomyelitis—and this whether the source of the organism employed was a case of osteomyelitis or a boil.

Spreading traumatic gangrene is often due to the *Streptococcus pyogenes.* Ogston found that injections of *staphylococci* might cause similar gangrene of the skin in animals. Koch induced a spreading gangrene in rabbits by injections of a little putrid blood, and in his cases only *streptococci* developed.

Lastly, these cocci may give rise to *inflammation stopping short of suppuration,* the streptococcus being associated with the *more diffuse* varieties. Cocci are frequently associated with inflammations about the fauces, even without the presence of pus. The evidence we have of the infective nature of papillary and ulcerative **endocarditis** is given in Chapter XI.

In the large majority of cases in which pyogenic cocci are introduced into the tissues only local results follow. In the presence of conditions favorable to the growth of the organisms they tend to spread. With especial ease they are carried to the lymphatic glands. There they become arrested and give rise to glandular abscesses. Thence, once more, their progeny and their products are distributed to more distant parts—it may be throughout the body (p. 281).

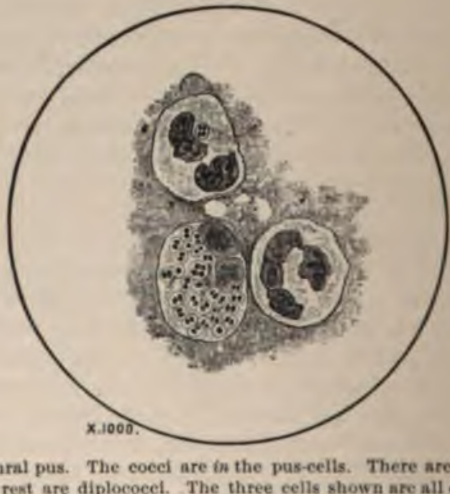
Erysipelas.—Micrococci have often been descried in erysipelatous skin, especially at the spreading edge. They occupy the lymphatic channels and spread along them: hence the name *infective capillary lymphangitis.* Orth produced typical erysipelas in a rabbit by subcutaneous injection of the fluid from an erysipelatous bulla; with œdema-fluid from this animal he successfully inoculated a second: the fluid and affected skin contained cocci in large numbers. He next cultivated the fungus, and produced erysipelas by injecting it. In 1881 Fehleisen found streptococci constantly present in pieces of skin excised from the *spreading edge* of an erysipelas-rash. The cocci filled the *lymphatics* of the *superficial part* of the corium, like an injection-mass, and occasionally extended to the subcutaneous fatty tissue, but were *never* found in the bloodvessels. Round-celled infiltration and dilated bloodvessels marked their presence; and in parts where the inflammatory zone had disappeared, the cocci had vanished also. The organisms were cultivated upon gelatine through fourteen generations in two months: eight out of nine rabbits, subsequently inoculated, suffered from the disease; and six out of seven inoculations upon man were equally successful. The incubation was fifteen to sixty hours; then followed rigors, fever, and typical rash. The evidence assigning a causal relationship to the streptococcus is therefore complete. Immunity, if conferred at all, did not last two months. Three per cent. solution of carbolic acid, or one per thousand of mercuric chloride, sufficed to destroy the vitality of the fungus.

Fehleisen stated that the *Streptococcus erysipelatis* presented distinct, though slight differences from the *Streptococcus pyogenes,* that it never caused suppuration, and that if an abscess occurred with erysipelas it was due to a mixed infection. The majority of recent writers upon the question have failed to detect either morphological or physiological differences, and are therefore of opinion that the two organisms are

identical, and that the point of inoculation, attenuation of the virus, and similar conditions must determine whether erysipelas or diffuse subcutaneous suppuration shall occur in any given case.

Gonorrhœa.—Neisser, in 1878, discovered in the urethral pus a large micrococcus (*Diplococcus gonorrhœæ*, or *gonococcus*, Fig. 169), peculiar to this disease. He recognized it by "facets" or flattenings on the surfaces in contact, such as are now known to occur in other rapidly multiplying cocci. It is distinguished from ordinary cocci by its smaller size; by the constant interval, about equal to the diameter of the coccus, between the individuals in the groups; and by the frequency of its occurrence *upon* and *in* the pus-cells. Neisser considered its presence a means of diagnosing gonorrhœal from other discharges. It was subsequently shown that the separation of the cocci is due to swelling of their capsules. It multiplies by fission in two planes alternately. In the first stage it is a diplococcus, each coccus having a bean-shaped outline. In the next stage each "bean" subdivides, and a tetracoccus is formed. The number of cells affected is always relatively small and varies in different cases. The coccus is cultivated with much difficulty. Cultures were

Fig. 169.



Gonococci from urethral pus. The cocci are *in* the pus-cells. There are two tetrads and two single cocci, the rest are diplococci. The three cells shown are all of the multinucleated variety. × 1000.

first carried out successfully by Bockhardt. This investigator injected a "fourth" cultivation into the urethra of a general paralytic, and produced a purulent discharge. The man died of pneumonia ten days later, and an examination of the urethra led Bockhardt to believe that the cocci probably pass through the epithelium into the lymphatics of the fossa navicularis, where they excite acute inflammation. They enter into white corpuscles, and either pass with them into blood-vessels, where they die, or come away in the pus.

Since then Bumm has succeeded in cultivating the gonococcus upon

solidified blood-serum; he inoculated a second and a twentieth culture upon a female urethra, causing typical gonorrhœa in each of the two cases. The proof of causation, thus placed beyond doubt, was difficult to obtain, as no animal is susceptible to the disease.

With regard to complications—suppurative lymphadenitis (*bubo*), an occasional occurrence in gonorrhœa, is said to be due to an infection of the glands by ordinary pyogenic organisms, the urethra in these cases being the seat of a mixed infection. The gonococcus, injected into subcutaneous tissue, does not cause suppuration, but disappears in twenty-four to thirty-six hours. It is, however, the only organism present in one-fifth of the cases of suppuration in the Fallopian tube (*pyosalpinx*).

The gonococcus may be present in joints, which are the seats of gonorrhœal arthritis: in some cases ordinary pyogenic organisms have been found, but in most cases none at all. It is quite unusual for gonorrhœal joints to suppurate. Gonococci have been found on the valves of the heart in endocarditis, and have been cultivated. Inoculation of the resulting cultures has produced gonorrhœa. The organisms have also been found in, and cultivated from, the blood; it appears capable in susceptible persons of giving rise to a general septicæmia. Inoculated on the conjunctiva it causes destructive inflammation (*gonorrhœal ophthalmia; ophthalmia neonatorum*).

The gonococcus is incapable of multiplying external to the body, except under special artificial conditions, as in a culture. Its resisting power is feeble and it soon perishes. If this were not so, considering the great frequency of the disease, infection otherwise than by contact would almost certainly occur.

Pneumonia (see Chapter XI.).—The production of acute pneumonia has been attributed to two distinct organisms. (1) The first, known as *Friedländer's pneumo-bacillus*, was first described by its discoverer as a coccus. He found great numbers of these organisms in the early stages of pneumonia, not only in the exudation, but also in the lymphatics of the lung and in the fluid of any pleurisy or pericarditis which was present. These bacteria are oval or rod-shaped; they are contained in oval or elliptical capsules with rounded ends. Two, four, or more organisms may be found in these capsules. The capsule is dissolved by alkalies and by water; is contracted by acetic acid (like mucin); is present only in the lung; is scarcely or not at all developed in cultures; and is best stained in cover-glass preparations by immersion for two or three minutes in a solution of gentian-violet in aniline water, followed by treatment with alcohol for half a minute. *The pneumo-bacillus does not retain the stain when treated by Gram's method.*

Friedländer subsequently cultivated the coccus in blood-serum, gelatinized meat-infusion, and on potato. Introduced by needle-puncture into the two former substrata, *the growth takes the very characteristic form of a round-headed nail;* on the latter ground it forms grayish drops, and subsequently a moist viscid layer. In a gelatine shake-culture it gives rise to bubbles of gas. Diffused in distilled water and

injected into the lung and pleura of rabbits, the organisms produced no effects; but of thirty-two mice inoculated, all died in less than twenty-four hours. The lungs were very red and almost universally solid, and the spleen was enlarged; both organs contained the characteristic bacteria, which were also present in considerable numbers in the blood, and in enormous numbers in some fluid which occupies the pleura. Guinea-pigs were more refractory to the poison, and, out of five dogs, only one suffered.

The pathogenic importance of these organisms is small, as they are only found in 5 per cent. of the cases of acute pneumonia. They occur also in some cases of membranous sore throat, and have been met with in abscesses in various parts of the body, in pleurisy, in otitis and rhinitis, and in endocarditis.

(2) Fränkel and Weichselbaum independently demonstrated the existence of another organism—*Fränkel's pneumococcus* or the *Diplococcus pneumoniæ*, which can be found in nearly all cases of pneumonia—especially acute croupous pneumonia. In cultures these organisms occur as round or oval cells, usually in pairs, but often in chains of four to ten or even twenty to thirty. These longer chains are much straighter than those of ordinary streptococci. In the tissues, the microbes often become lancet-shaped, and their pointed ends may be toward or away from each other, usually the latter. These cocci have capsules just like Friedländer's, and they may be similarly stained. *They retain the aniline stain when treated by Gram's method.* Whereas Friedländer's bacillus can be readily cultivated on gelatine at 70° F., Fränkel's is best grown on blood-serum or blood-agar at a temperature of 95° F. to 98.5° F.; and *the growth is scanty and not nail-shaped, but of characteristic "dew-drop" form.* When the organism is grown on gelatine this medium is not liquefied. In many of its characters it thus resembles the Streptococcus pyogenes. The substratum must be kept slightly alkaline or growth ceases. Even when transferred daily from tube to tube the diplococcus rapidly loses its virulence. To preserve or to restore its pathogenic power, an occasional inoculation upon a susceptible animal must be resorted to. Cultivation for one or two days at 107° F. destroys its virulence, which is weakened by longer cultivation at slightly lower temperatures.

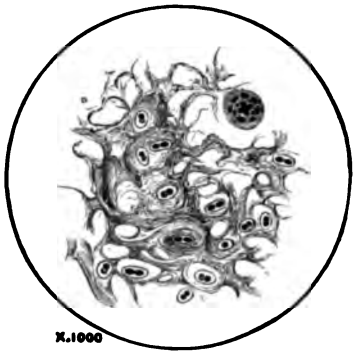
Subcutaneous injections of virus of *full intensity* into rabbits, mice, and guinea-pigs cause an acute, generally fatal, illness, like septicæmia, with characteristic post-mortem appearances; but there is no sign of pneumonia. An *attenuated* culture introduced beneath the skin does sometimes give rise to pleurisy or pneumonia, or both; and *these diseases usually follow injection of such a culture into the lungs.* In such cases the appearances closely resemble those in pneumonia and pleurisy in man, and the exudation contains large numbers of encapsuled cocci. Pericarditis also may ensue. These results show that the effects vary with the virulence of the parasite according to the usual rule (p. 286). This conclusion may be illustrated by the reaction of different species of animals. In those least immune septicæmia is usual; in those more

immune a local reaction, such as acute pneumonia. When the virulence of the organism is very low, only broncho-pneumonia may follow.

The inoculation either of filtered cultures of the organism, or of the serum of animals vaccinated with them, is said to confer a temporary immunity. Issaeff asserts that the cocci thrive in cultures treated with the "immunized serum," showing that this serum is not bacteriolytic. It apparently possesses "opsonic" properties (p. 294). Sputum *before* the "crisis" is virulent; but sputum *after* the "crisis" is said to confer immunity; in other words, the cocci have become "attenuated."

Besides being present in the lung, the cocci are occasionally found in the blood and spleen, and in inflammations arising during the course of pneumonia, or even independently—pleurisy, empyema, meningitis, endocarditis, peritonitis, and otitis media. Moreover, it appears to be an *occasional* denizen of the mouth and nasal cavities, also occurring in the saliva and in the middle ear of healthy people. It would seem that the organism remains innocuous until some circumstance, such as chill,

FIG. 170.



Diplococci pneumoniæ entangled in the meshes of the fibrinous exudation. From a section of lung in the "red hepatization" stage of acute pneumonia. In the upper part of the field is a cell containing several cocci—possibly a phagocyte. × 1000.

exhaustion, or intercurrent disease, enables it to gain a footing in the tissues and manufacture its toxins. Pneumonia does not follow inoculation in the lower animals unless the parasite is localized in the lung. Salvioli says that he succeeded in inducing lobar pneumonia in guinea-pigs by intra-tracheal injection of pneumonic exudation containing these cocci; but Fatichi failed with rabbits.

When pneumonia runs on to suppuration and gangrene these complications are possibly due to a secondary infection by the Staphylococcus pyogenes aureus or Streptococcus pyogenes, but the pneumococcus itself is a "pyogenic" organism.

Cerebrospinal Meningitis.—The *Meningococcus* or *Diplococcus intracellularis meningitidis* was originally described by Weichselbaum, and is now generally recognized as the cause of epidemic cerebrospinal meningitis. It is also asserted by Still to produce the posterior basic meningitis of infants. It is a diplococcus without a capsule, and is

found principally within the multinuclear leucocytes of meningeal exudation, though some organisms lie free in the fluid. It has been described also as occurring rarely in blood, pus, consolidated lung, and nasal mucus. It must be borne in mind, however, that some confusion has at times existed between this organism and the pneumococcus. The meningococcus is stained by the ordinary aniline dyes; it is decolorized by Gram's method. It grows well on Lœffler's blood-serum, forming round, whitish, viscid-looking colonies, clearly defined, and attaining a diameter of 1–1½ mm. in twenty-four hours (Councilman). In cultures it soon dies out, but it appears capable of resisting drying, and is easily carried by currents of air. This fact accounts for the occurrence of the disease in epidemic form. Cultures injected beneath the spinal membranes of goats produced typical meningitis. Harris (quoted by Osler) recommends for the isolation of the organism that the fluid should be "plated" with alkaline 5 per cent. glycerine agar, by which means the colonies of the meningococcus may be easily separated from other organisms, with which it is sometimes found associated. In chronic cases of the disease, no organisms may be found in the cerebrospinal fluid.

Malta Fever.—This disease, called also Mediterranean, or undulant, fever, is caused by a small oval coccus (*Micrococcus melitensis*), discovered by Bruce. The organism may occur singly or in pairs, but does not form chains. It is non-motile, and can be grown on slightly alkaline artificial media. It is decolorized by Gram's method. The serum of patients suffering from Malta fever agglutinates the cocci, even when it is considerably diluted (1 : 200).

Rheumatism.—Many observers have found organisms in the blood of rheumatic patients, those most frequently noted being streptococci. These organisms were first described by Apert and Triboulet (1898), and their causal relation to rheumatic fever has been carefully investigated in this country by Poynton and Paine. Injections of these cocci into animals have produced articular lesions, endocarditis, and pericarditis; and in some cases spasmodic twitching of muscles, supposed to be analogous to chorea. The specific nature of these organisms and their relation to rheumatism must at present remain undecided.

For the bacteriology of **Syphilis**, see Chapter X.

Micrococci have been described in *Scarlatina*, *Measles*, *Vaccinia*, *Variola*, *Typhus Fever*, *Acute Yellow Atrophy of the Liver* (*early stage*), *Whooping-cough*, and many other diseases, but the evidence in favor of their causal relationship to the respective diseases is not sufficient to justify a description of them here.

FIG. 171.

Sarcinæ ventriculi. × 500.

Micrococci which divide in three diameters, at right angles to each other—**Sarcinæ**—are often found in vomit from stomachs dilated from pyloric obstruction and in cases of dyspepsia from chronic catarrh (*Sarcina ventriculi*) (Fig. 171); in the bronchi and deeper parts of the lungs in phthisis

(*Sarcina pulmonum*), and in the urine (*Sarcina urinæ*): they have been seen also in abscesses and in blood. Single cocci may be seen, but the majority form cubical groups of four (Fig. 171). S. urinæ (2.5 μ) is larger than S. ventriculi, or than the fungus of this shape occurring in the lungs (1 μ to 1.5 μ). Sarcinæ may occur in the stomach without appearing in the urine or elsewhere. It is extremely difficult to get rid of these fungi when they are once established. The nature of the decomposition to which they give rise is unknown.

FIG. 172.

Bacillus anthracis and Bacillus typhosus, to show large size of former. × 500.

II. Bacilli.—The members of this group are straight slender rods, the ends of which may be rounded, square, or slightly cupped. They multiply by transverse division, and often grow into long, jointed, but unbranched filaments, without constrictions at the joints. Formation of spores has been detected in some species.

The **Bacilli** of **Tuberculosis, Leprosy, Glanders,** and **Rhinoscleroma** are described in separate sections dealing with these diseases. (See Chapter X.)

Bacillus Anthracis.—The bacillus of anthrax or splenic fever was the first bacterium to be discovered (Daviane, 1850), and was for a long time the best known of all the parasitic fungi. If the blood from the spleen of animals that have died from this disease be examined, enormous numbers of these organisms will be found. The bacilli are large rods averaging about 8 μ long by rather more than 1 μ broad (Fig. 172). They are straight and motionless, and have slightly concave ends (Fig. 173). In a suitable culture-material, such as ordinary agar or gelatine media, with a plentiful supply of oxygen and a temperature of between 65° F. and 90° F., the rods grow into long interlacing filaments grouped into convoluted bundles not unlike a mass of fine hair. In these filaments, spores may be formed at regular distances; later on the bacilli break up and the spores are set free. Under favorable circumstances these grow into bacilli. In living animals, where the supply of oxygen is not sufficiently plentiful, the long filaments and spores are not found, but the rods multiply rapidly by division. In a stab-culture, the growth takes the form of an innumerable number of branched spikes jutting out transversely from the line of puncture (Fig. 174). The bacilli retain the stain when treated by Gram's method. They are readily destroyed, succumbing to the action of gastric juice and to putrefaction: the spores are unaffected by either of these influences, and are among the most resistant organisms known. They may be separated by filtration, washed with distilled water, alcohol, and ether, and then dried; but,

FIG. 173.

Bacillus anthracis, with spores, free and in the interior. × 1000.

notwithstanding all this, they will still, under favorable circumstances, develop into bacilli, and, when inoculated, give rise to splenic fever. The products of the anthrax-bacillus have been already discussed and tabulated (p. 279). Other facts regarding it have been given in the earlier parts of the present chapter.

Fig. 174.

Bacillus anthracis. Stab-culture in nutrient agar-agar.

Animals vary enormously in their susceptibility to anthrax-bacilli. Those most susceptible, such as white mice and guinea-pigs, die from splenic fever a few hours after inoculation; whilst those least susceptible, such as white rats and Algerian sheep, remain unaffected. In man, who is to a moderate extent susceptible, the disease is at first local, but soon becomes generalized.

In *animals* that have died of splenic fever, the spleen is much enlarged, the glands, nearest the point of entry, are swollen, and cloudy swelling is universally present. The bacilli exist in enormous numbers in the capillaries of the spleen, and to a less extent in those of the lungs, liver, kidneys, and intestine (Fig. 154). Numbers of bacilli are discharged from the body in the urine, fæces, and blood flowing from the nose and mouth of the animal before it dies; thus the ground in its neighborhood becomes covered with the organisms and is, therefore, highly infectious. In warm marshy districts the bacilli multiply and sporulate. The spores may be carried by water or other means to meadows where anthrax has not previously occurred. Sheep and cattle are infected while grazing. Pasteur considered that the mouths of the animals were wounded by siliceous grasses, and believed that the cuts thus made became inoculated with bacilli or spores. In favor of this view he quotes the frequent swelling of the cervical glands in sheep affected by this disease; but both animals and man are frequently infected by insects which bite them on the face. According to Koch, the intestine is the commonest seat of infection.

If the bodies of the dead animals are buried at a depth of one metre or more, where there is neither oxygen nor a suitable temperature, no development of spores occurs and the bacilli die.

In *man* infection may occur (1) through the skin, and (2) through the mucous membrane.

(1) Infection through the skin occurs especially in those who work with raw hides. The bacilli give rise to a characteristic local lesion (*malignant pustule*), consisting of a central, black, necrosed area surrounded by vesicles and a hyperæmic zone, the base of the whole mass being œdematous. If the pustule be excised at an early stage, the generalization of the disease may be prevented, although cases are on

record in which a month after excision of the pustule such patients were still eliminating bacilli in the urine.

(2) Infection not infrequently occurs through the mucous membrane, especially the respiratory (*woolsorters' disease*), from inhalation of spores or bacilli with the dust from infected wool. In these cases the local lesions occur in the mucous membrane of the large bronchial tubes. Considerable swelling of the bronchial and mediastinal glands follows, and not infrequently effusions of fluid may occur into the pleura or pericardium. Such patients die more rapidly than in the case of malignant pustule, with symptoms of acute septic poisoning, though after death but few bacilli can be found in distant organs.

Immunization.—Pasteur cultivated the bacilli for twenty days at a temperature of 108° F. and inoculated sheep and cattle with the resulting organisms, later on repeating the inoculation with less attenuated bacilli, and finally with ordinary virulent cultures. In this way he rendered many animals for a time immune. The method is, however, open to the disadvantage that an appreciable proportion of the animals thus treated died of splenic fever. A safer method is to inject the animal first with some "immune" serum along with the attenuated bacilli (Sobernheim). The attenuation of anthrax-bacilli has also been brought about in other ways—by cultivation under a pressure of eight atmospheres, by the addition of small quantities of antiseptics to the culture-medium, or by the passage of the organisms through the bodies of certain animals. The attenuation is not accompanied by any morphological change, and the virulence of the bacilli may be restored at any time. Some good results are recorded in cases of anthrax in human beings from the use of anti-anthrax serum; it is not quite clear whether this is mainly antibacterial or antitoxic.

Bacillus Typhosus.—This organism, which is sometimes spoken of as *Eberth's bacillus*, is the causal agent of typhoid fever. (See Chapter XI.) The bacilli can, with some difficulty, be found during life in the fæces, spleen (obtained by puncture), and urine. After death, if the parts are removed without delay, the organisms can be easily discovered in the spleen, liver, mesenteric glands, kidneys, and recent lesions in the intestines. Their presence can be more readily ascertained by inoculating a culture-ground with a piece of the suspected organ, preferably the spleen or liver, than by examining stained sections under the microscope.

In appearance typhoid-bacilli are not unlike tubercle-bacilli. Their breadth is about a third of their length, which varies between 2 μ and 3 μ. Thus, they are a little thicker than tubercle-bacilli, while their ends are distinctly rounded. They stain slowly with aniline dyes, and part with color easily. The best stains are probably Loeffler's methylene-blue and Ziehl's fuchsin stain (p. 301). They do not retain the color when treated by Gram's method. Clear spaces often occupy the centre of the rods. There is some doubt as of the formation of spores. A typhoid-bacillus, when stained by special methods, appears enveloped by a thick capsule. In intimate connection with this capsule,

apparently composed of the same substance, and distributed over its whole surface, are the flagella, eight to twelve in number, varying much in length and thickness. Sometimes they are considerably longer than the parasite itself. Some of the bacilli have only a single flagellum at one end (Fig. 175).

Cultures can be readily obtained. The organism thrives in milk, which it does not coagulate, and can even multiply for a short time in sterilized drinking-water—points of practical importance. It thrives best at the body-temperature, but will grow readily at 60° F. It does not liquefy peptone-gelatine, but a *stab*-culture appears on the surface as a flat, spreading, white film, with a wavy margin, and marks the line of puncture by a growth with an irregularly wavy outline. A *streak*-culture on gelatine (Fig. 176) forms a narrow white line along the track of the needle. It is mainly aërobic. Potato-cultures of this bacillus are almost invisible: this fact is utilized in the recognition of the organism. Thus, if a fresh potato-

FIG. 175.

Typhoid-bacilli, showing flagella. × 1000.

culture be incubated for forty-eight hours, *no visible change* occurs; but if surface-scrapings be then taken, stained, and examined, threads of the bacilli will be easily found. Many peculiarities of growth are described in order to distinguish it from other bacteria, especially the *Bacillus coli communis*, which it closely resembles both morphologically and in its mode of growth and habitat. Thus acid-products, but *no indol*, are formed in bouillon-cultures, while most bacilli, occurring under the same conditions, form indol. Another suggested test depends on the tendency which this organism possesses of *absorbing the color*, when cultivated on a gelatine-medium stained with gentian-violet, thus leaving the gelatine colorless. Still another is founded on a slight indifference which the organisms show to the action of carbolic acid. Thus, if a minute quantity of carbolic acid (2.5 per 1000) be added to a culture of mixed organisms, the growth of most will be arrested, but that of the *B. typhosus* and the *B. coli communis* will continue. The chief points by which the latter organism can be distinguished from the typhoid-bacillus are tabulated on page 321.

According to Sternberg, ten minutes' exposure to moist heat at 140° F. destroys typhoid-bacilli. They are also killed in about the same time by the action of gastric juice.

Inoculation has hitherto been only partially successful. It is doubtful if any animal is susceptible to typhoid fever as we know it in man. Rabbits, dogs, and mice have been inoculated, and have died in thirty-six hours with symptoms of general septicæmia; but though, when virulent cultures are used, an enlarged spleen and swollen Peyer's patches have been very generally found, the disease never runs a longer course, nor is there ever any characteristic ulceration. Very rarely suppuration may be due to this organism, *e. g.*, periostitis, though in most cases in which pus occurs in typhoid fever it has been found to contain other organisms. There is a marked difference in the effects produced if the filtered products be alone injected. These give rise to no marked lesion beyond fatty degeneration of the heart (S. Martin). If the dead bodies of the bacilli be also injected, the effect is much more marked. The toxines of the bacillus are, therefore, in all probability intracellular; but their real nature is unknown. They appear to exert their effects specially on the lymphoid cells, as is seen in the necrosis of Peyer's patches, the enlargement of the spleen, and the diminution in the number of leucocytes in the blood which accompanies the disease.

Typhoid-bacilli leave the body of an infected person in the fæces and urine. They may be conveyed to other susceptible hosts by drinking-water or by food (uncooked), and they may probably be carried directly by the air to the mouth or respiratory passages. Oysters and other shell-fish may be contaminated with sewage containing typhoid excreta, and may thus, when eaten raw, give rise to the disease.

It is generally stated that the bacilli settle in the lymphoid tissue of the intestine, giving rise to local lesions, and there forming toxines. Against this view must be set the fact that the organisms can generally be found in the blood in the early stages of the illness, suggesting that the condition is a "septicæmia" or generalized infection, the toxines especially affecting the lymphoid tissue of the intestine.

Immunization.—It has been repeatedly shown that mice, guinea-pigs and other animals can be immunized against the effects of the typhoid-bacillus by the subcutaneous injection of dead cultures of the organism. It has also been shown that, although the animals can be thus protected against the action of typhoid-bacilli, they are not protected against the effects produced by the injection of the toxines derived from the bacilli. In the same way, while the serum of healthy persons is somewhat inimical to typhoid-bacilli, that of convalescents from typhoid fever has been found to have a far more marked action. That this serum is antimicrobic and not antitoxic has been shown, among others, by Pfeiffer, who added to the toxines serum from persons convalescent from typhoid fever, and injected the mixture into guinea-pigs, at the same time injecting a corresponding series of guinea-pigs with the

typhoid toxine alone. The results in both series were precisely similar. The results obtained in enteric fever by the use of antityphoid serum prepared from animals have been disappointing.

It has been found that if the serum of animals immunized to the typhoid-bacillus, or of persons convalescent from typhoid fever, be added to an active culture of typhoid-bacilli, the organisms lose their mobility and become aggregated into clumps of various sizes (*Widal's reaction*). Their vitality is, however, not destroyed, although their virulence is apparently diminished. This "agglutination-reaction" (see p. 298) is much used as an aid in diagnosis. For this purpose it is necessary to withdraw a small portion of the blood of the suspected patient, and to observe the effect produced by the serum thence obtained upon the bacilli contained in a selected culture. In order to ensure reliable results it is necessary that the typhoid bacilli be carefully selected and as carefully reared; and, on the other hand, that the serum be diluted at least twenty times, and the diagnosis based on the appearances observed within the first twenty minutes of preparing the mixture, as normal serum, without these precautions, may give a similar reaction. More trustworthy results are obtained by still further diluting the serum (1 : 50) and allowing a time-limit of half an hour.

As a protective vaccination against typhoid fever, dead cultures, similar to those injected into animals for the purpose of immunization, are employed (Wright). A local inflammatory action with slight fever generally results. As one attack of the disease does not produce immunity to subsequent infection, it is not to be expected that entire protection will be conferred by inoculation; but statistics are in favor of the method as conferring some degree of immunity.

Bacillus Coli Communis. (*Bacterium coli commune.*)—This bacillus is a common denizen of the intestine, and especially of the neighborhood of the cæcum. It is also found in the mouth, and occasionally in other parts. It very rarely occurs alone. In size, in shape, in the possession of flagella, and in staining-reactions, this organism very closely resembles that of typhoid fever. According to some observers, the B. coli communis has fewer flagella, but this supposed peculiarity is certainly not constant. There is a tendency for the bacilli to occur in pairs, and, when cultivated, in short threads. This organism probably does not form spores. It is mainly aërobic, and seems to have a slight power of active movement. Like the typhoid-bacillus, it grows best in acid media; but the surface-colonies are larger, denser, and more glistening, as well as of a pale brownish tint; while a streak-culture forms a broad dense growth stretching out on both sides of the track (Fig. 177). In gelatine stab-cultures it assumes the form of an irregularly encrusted stick, with small outgrowths here and there, but without tapering in either direction.

There can be no doubt, on the one hand, that this organism exists in perfectly healthy intestine; nor any doubt, on the other, that it is met with in a large number of morbid conditions. Thus, it may apparently give rise to otitis media, to osteitis or periostitis, and to

general suppurative peritonitis. It appears to vary much in virulence according to circumstances.

The most important distinctions between the *B. typhosus* and the *B. coli communis* may be thus tabulated:

B. typhosus.

1. Actively motile.
2. When "streaked" on surface of gelatine forms a narrow white line of growth along the track of the needle (Fig. 176).
3. In gelatine "shake-culture" produces no gas.
4. On potato forms an almost invisible transparent white film.
5. Does not curdle milk.
6. Does not produce *indol* in peptone-broth-cultures.
7. Reacts with serum from patients with typhoid fever.

B. coli communis.

1. Sluggishly motile.
2. When "streaked" on surface of gelatine forms a broad dense growth spreading out on both sides of the track (Fig. 177).
3. In gelatine "shake-culture" produces bubbles of gas.
4. On potato forms a thick slimy yellowish or brownish growth.
5. Curdles milk in about 48 hours.
6. Produces *indol* in peptone-broth-cultures.
7. Does not react with serum from patients with typhoid fever.

Fig. 176.

Bacillus typhosus. Streak-culture on nutrient gelatine. (See p. 303.)

Fig. 177.

Bacillus coli communis. Streak-culture on nutrient gelatine. (See p. 305.)

The **Paratyphoid Bacillus** is an organism belonging to the same group as the typhoid-bacillus and the *B. coli*, but differing slightly from both of these. It is capable of producing a disease almost exactly

resembling enteric fever, from which it is distinguished mainly by the failure of the patient's serum to exhibit the agglutination reaction with typhoid bacilli. Two varieties of the organism are described.

Bacillus Diphtheriæ.—In 1883 Klebs drew attention to a bacillus which he had found constantly present in diphtheritic membrane. In the following year Löffler published an account of its morphology and cultivation, together with results obtained by inoculation. The bacillus is therefore often called the *Klebs-Lœffler bacillus.*

The bacillus is to be found in nearly all cases * diagnosed clinically as diphtheria, as well as in some nasal discharges, and not infrequently on the fauces of otherwise healthy persons. In diphtheria it is usually limited to the false membrane and its neighborhood, and grows most abundantly in the more superficial parts of the membrane; on those rare occasions in which it has been found in an internal organ, it has probably reached it from the blood-stream, to which it may have gained access only a few hours before death. Its presence in the membrane can be made out during all stages of the disease; and the examination of scrapings from the mucous surface of the mouth shows that it may continue to live for many weeks after the fever has disappeared. Bacilli having a close morphological resemblance to it seem to be occasionally present in the mouths of healthy individuals, as well as organisms giving even the same culture-results as the diphtheria-bacillus. The term *pseudo-diphtheria-bacillus* is applied to these forms, some of which, at any rate, seem just as pathogenic as the more orthodox organism. Bacilli taken from diphtheritic membrane can be cultivated through many generations, and after an interval of some months are still capable, when inoculated, of giving rise to the original disease—not merely to the local inflammation and membrane, but also to the subsequent paralysis.

The diphtheria-bacillus is generally rather shorter and thicker than the tubercle-bacillus. It is usually from 1.5 μ to 2.5 μ long, and about a third as broad. It may occasionally attain a length of 6 μ to 8 μ, both in the membranes and in cultures. Its shape is not always regular; sometimes the ends are thicker than the centre, and sometimes the centre than the ends. The latter are rounded. The bacilli not infrequently contain a row of two or three highly refracting areas, the nature of which is unknown. In all probability they are *not* spores. The organism is believed to multiply by fission only. It never forms long threads; it is motionless. The B. diphtheriæ stains readily with aniline dyes, and retains the stain when treated by Gram's method. The organisms exhibit a tendency to "polar staining," which has been held by some observers to be very characteristic of this bacillus.

FIG. 178.

Bacillus of diphtheria. × 800.

The organism can be cultivated in many media. It does not liquefy

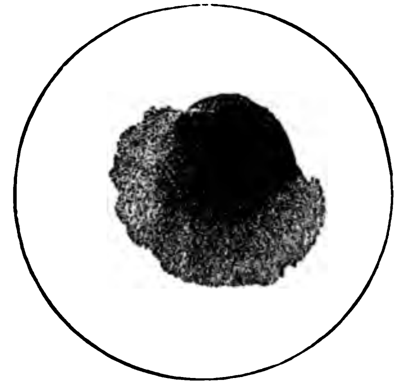
* Some authorities limit the name of "diphtheria" to those cases in which it can be found.

gelatine. It grows well in milk; but the most frequently employed culture-ground is blood-serum. A minute portion of membrane

FIG. 179.

Bacillus diphtheriæ. Streak-culture on blood-serum. (Lœffler.)

FIG. 180.



Bacillus of diphtheria. Colony on agar twenty-four hours after inoculation. × 100. (After Fränkel.)

transferred to this will develop, in the course of twenty-four hours, small gray elevated discs with pale circumferences (Fig. 180). In secondary cultures these show a tendency to become arranged in lines (Fig. 179). Growth can take place at any temperature between 70° F. and 108° F., but is most luxuriant when it remains between 92° and 99° F. Moist heat of 140° F. is rapidly fatal, but dry heat at 208° F. may take an hour to destroy the organism. A free supply of oxygen encourages, but is not essential to, its growth. There is no difficulty in maintaining the virulence of the organism during cultivation; but if a culture be left undisturbed for some months its virulence diminishes, and this result follows more rapidly if it be allowed to become acid. In either case replantation into a fresh culture-ground rapidly restores the virulence. The organism resists drying to a much greater extent than is usual in bacilli which do not form spores. If a specimen be dried and kept dry for six months, it will grow as soon as it is placed under favorable conditions. This point is of great practical importance, and emphasizes the necessity for thorough disinfection. Cultivation of the organism in the presence of sewer-gas does not increase its virulence (Shattock). The accredited influence of sewer-gas in the production of diphtheria must therefore depend upon its direct effect upon the host.

From the foregoing account it will be seen that the requirements of the organism as regards air, temperature, and moisture are admirably provided for in the mouth and upper air-passages. Moreover, they are supplemented by the co-operation of various cocci, especially the pyogenic varieties, which are always ready to hand. The spread of the

membrane inward is probably due partly to the more suitable temperature and partly to the force of inspiration. The cat is the only animal besides man that is liable to true diphtheria.

In 1890, by means of filtration through porcelain, and subsequent precipitation with absolute alcohol, Roux and Yersin succeeded in isolating, from cultures of the organism, a poison which, if injected into animals in large doses, caused prostration and death, but, if in small doses only, paralysis and albuminuria (in rabbits on the fifth day). In no case was any membrane formed. It was also noted that the addition of acid to the poison rendered it harmless. They believed this poison to be an "unformed ferment."

Two years later, by very similar procedures, Sidney Martin separated identical series of substances (1) from the tissues of persons dead of diphtheria; and (2) from cultures of the organism on media closely resembling the tissues in chemical composition. This series consisted of hetero-albumose, proto-albumose, deutero-albumose, and an organic acid. Of these, the first was only to be obtained from the membrane and the last from the tissues; the proto- and deutero-albumoses were present in both membrane and tissues. Martin showed that the factory of the albumoses was the tissues, and especially the spleen, and that but little was formed at the site of the membrane. He regarded all the products as the result of a ferment produced at the seat of the local disease, and thence entering the circulation. He considered that the paralytic effects were due to the action of the albumoses on the peripheral nerves, which caused breaking up of the myelin sheath, and more or less thinning and even disappearance of the axis-cylinder; fatty degeneration of the heart and voluntary muscles was also found.

The nature of the toxines is, however, only partly known. It is certain that toxines can be formed even when the bacilli are grown in a medium free from proteid; while other observers have separated from cultures a toxic body giving no proteid reactions. It is possible, therefore, that the bodies which Martin separated only *contained* the toxines, and that these have not yet been isolated and described.

Immunization.—Another step in advance was made in the same year (1892) by Behring, who drew attention to the acquired immunity which could be obtained against these diphtheria-bacilli. He described four ways by which animals could be rendered immune. He injected (1) cultures of the bacillus attenuated by heat; (2) cultures attenuated by the addition of trichloride of iodine; (3) the pleural exudation of animals dead of experimental diphtheria; or (4) a dose of virulent diphtheria-bacilli, followed by one of trichloride of iodine. He next showed that the addition of some serum, from an animal thus immunized, to an ordinary culture of the organism not only arrested the action of the bacilli but neutralized the poison as well, so that, when injected, it was found to be innocuous. The final stage was reached when he showed that, if a fatal dose of diphtheria poison had been injected, it could be neutralized by a subsequent injection of this

"immunized serum." A good deal was found to depend upon the method employed for rendering immune the animal from which the serum was taken. Within certain limits, the injection of small amounts, spread over a long period, was found to give the best results. In cases in which only the filtered culture and not the actual bacilli are employed, the dose of serum required is found to vary not only with that of the poison, but also with the body-weight and possibly with the species of animal employed. Again, the doses requisite depend upon the interval between the two injections. These results have led to the extensive use of the immunized serum for therapeutic purposes; these have been more fully referred to in the section on Immunity (p. 287).

Bacillus of Influenza.—In 1892 Pfeiffer, Kitasato, and Canon succeeded in finding a minute bacillus, which is now generally believed to be the cause of this disease. It is extremely minute, measuring 0.3 μ by 0.1 μ. It stains with Ziehl's and Löffler's fluids; the ends take the stain best, and thus the organism often looks like a diplococcus. It does not retain the stain when treated by Gram's method. It occurs singly, in pairs, and in short chains. It is non-motile and does not form spores. Large numbers have been found in the bronchial secretion: they persist for some weeks after the catarrh. It has been found in the peribronchial tissue, and on rare occasions in the blood. Complications in influenza are generally associated with the presence of other bacteria.

Pure cultures are not easily obtained. On sugar-agar these appear as small, discrete, transparent globules visible only with a lens. The bacillus is aërobic, grows best at the body temperature, and is easily destroyed by drying.

Local inunction of pure cultures into the respiratory mucous membrane of monkeys and rabbits is followed by the characteristic symptoms, but as the bacilli do not multiply in any of the lower animals, the resulting condition is probably due to the absorption of toxines.

Bacillus of Plague. (*Bubonic Fever.*)—Kitasato and Yersin discovered this bacillus during an epidemic at Hong Kong in 1894.

They succeeded in finding bacilli in the blood, buboes, and internal organs, especially the lungs of the plague-stricken patients. The organisms stained readily with the usual reagents; they had rounded ends, which appeared darker than the central parts; they possessed flagella and slight power of movement. No spores were discovered. The organisms were easily destroyed by sunlight, heat, carbolic acid, and quicklime, but resisted drying for four days. Similar organisms were never found in healthy persons or in those suffering from any other disease.

Cultures were obtained on blood-serum, glycerine-agar, and other media. The colonies were whitish-gray, rounded patches, with uneven edges. In the cultures the bacilli often formed long threads.

Mice, rats, guinea-pigs, rabbits, and monkeys, if inoculated with pure cultures or with blood from patients, succumbed with a constant

sequence of symptoms. Roughly speaking, these appear to have corresponded to those in man, though the enlargement of the glands does not seem to have been so marked. The bacilli were found in the blood, glands, and organs of these animals. Pigeons are immune. Animals fed with the organism or infected blood died in the same way as those inoculated; and in man infection is stated to occur by the alimentary tract. The position of the bubo in the groin, however, suggests an entrance by the skin of the legs. The disease has often been conveyed from one district to another by means of infected rats.

That the bacillus is the cause of the disease was sufficiently proved by the death from plague of an attendant in a laboratory at Vienna where experiments were being carried out on some cultures sent from India.

Immunization.—Rabbits have been rendered immune by the injection of sterilized cultures, and an antiplague serum has been prepared from horses treated in a similar manner (Yersin). An antitoxic serum has also been prepared (Lustig). Haffkine's *preventive inoculation*, which is better known, consists in the injection of a bouillon culture sterilized by exposure to 70° C. for one hour.

Bacillus of Tetanus.—In 1884 it was shown that tetanus was an

FIG. 181.

Bacillus of tetanus. For description, see text. × 1200.

inoculable disease. In the same year a special bacillus was described, but it was not isolated and cultivated until 1889. Kitasato accomplished these results by heating the impure cultures of pus, obtained from the original wound, to a temperature of 80° C., and then incubating the residue in an atmosphere of hydrogen.

The size of the bacillus is from 3 μ to 5×0.4 μ. The bacilli are often arranged in longer spiral threads. Spores are often found. They occupy one end of the bacillus, and being two to four times the diameter of the organism, give it the appearance of a miniature drum-stick (Fig. 181). Flagella are attached to the ends and sides, but the organism is only slightly motile. The bacillus can be stained by the usual methods. Its habitat seems to be the superficial soil, especially when mixed with manure, from which it can often be obtained.

It can be readily cultivated if great care be taken to exclude oxygen; this bacillus and that of malignant œdema are the two most prominent examples of anaërobic organisms. It can be separated from the other organisms with which it usually occurs by heating the impure culture to 80° C., which will kill all the organisms but the spores of the tetanus-bacillus. The organism liquefies gelatine slowly, and grows only beneath the surface, forming thin waved lines radiating from the puncture-track. The most suitable temperature is 97° F. to 100° F. The cultures have a characteristic odor and appearance (Fig. 182), The spores are noted for the great resisting power they show to the ordinary methods of destruction. Thus, they have been known to resist successfully *boiling* for five minutes, *drying* for five months, and immersion in *carbolic acid* (1 : 20) for ten hours, and in *mercuric chloride* (1 : 1000) for three hours. Fifteen minutes' boiling is invariably fatal. For a long time all attempts at attenuation failed, but it has been shown by Tizzoni and Cattani that attenuation results from (1) the exposure to the air of spores on threads; and (2) the preservation of cultures in various gases for long periods—generally over a year.

FIG. 182.

Tetanus bacilli. Stab-culture in nutrient sugar-agar.

The constant presence of the bacillus in cases of tetanus, and the possibility of purifying it by cultivation having been established, it remained for Kitasato to complete the proof by successfully inoculating these cultures on animals. He showed not only that inoculation of the bacillus produces the disease, but also that in such cases the organisms remain confined to the wound, and that the symptoms are due to the absorption and circulation of their products. Thus, he found (1) that inoculation of a *sterilized* culture produced a fatal form of the disease, but that no bacillus could be found in, and no cultures obtained from, the organs of an animal killed in this way; (2) that inoculation of the spores with some mechanical irritant, but without bacilli or toxines, produced a similar disease, and, similarly again, that no bacilli could be found in, and no cultures obtained from, the *distant* organs; and (3) that in the latter case the symptoms were first observed in the locality of the inoculated part. He concluded, therefore, that the bacilli in the wound produced their effect by manufacturing poisons which are gradually disseminated.

The nature of these toxines is unknown. Martin has separated, from the tissues of persons dead of tetanus, two bodies; one of these contains proteid, the other does not. Brieger has also separated a non-proteid body. According to both these observers, a non-proteid body is the toxine which acts as a direct excitant of the motor-cells of pons, medulla and spinal cord, and thereby produces the muscular spasms characteristic of the disease. The chief reason for the belief held by

many, that some ferment acts as an intermediary between the bacillus and the toxines, lies in the extremely definite incubation-period which exists between the introduction of the bacterial products and the onset of the symptoms, and which gives time for the production of secondary toxines from the tissues. On the other hand, it has been maintained that the poison is absorbed by the peripheral nerves and has to travel along them to the spinal cord before it can produce symptoms of poisoning. The incubation period is thus possibly associated with the length of the route traveled by the toxine. Time is also necessary for the combination of the poison with the main bodies of the cells even after it has attached itself to their receptors. The action of the poison is to exaggerate the irritability of the cells of the spinal cord, so that violent convulsions are caused by small stimuli. The bacilli also manufacture a substance (tetano-lysin) which has the power of destroying red blood-corpuscles.

Immunization.—Kitasato conferred a two-months immunity on rabbits by injecting a small portion of a sterilized (filtered) culture, followed by five daily injections of trichloride of iodine (3 c.c. of 1 per cent. solution). Subsequent observers have obtained results precisely analogous to those already described in diphtheria. Small but regularly increasing (3 c.c. to 120 c.c.) and repeated doses of the filtered cultures gradually confer immunity; and the serum obtained from animals thus protected is found to prevent the development of symptoms if injected *before*, or *with*, a fatal dose of the toxines. It is doubtful whether the serum can exercise a curative action when the symptoms of the disease have developed, the poison being then firmly united to the cells. Good results are claimed from its use as a prophylactic. It is antitoxic, not antibacterial.

Malignant Œdema.—A spreading œdema ending fatally may be produced by the inoculation of mice, guinea-pigs, or rabbits with garden-mould. Only one form of bacillus develops, and the œdema-fluid containing it is infective (p. 284). The bacillus is 3 μ to 3.5 μ in length, but grows into longer threads, which much resemble anthrax-bacilli. They differ in showing no segmentation, in having rounded ends, and in being absolutely anaërobic. The bacilli bear spores, but do not retain the stain in Gram's method. In cultures, characteristic air-bubbles occur at the sides of the tube.

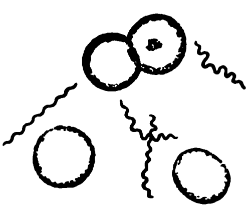
Dysentery.—Some forms of dysentery are due to a bacillus, *B. dysenteriæ*, discovered by Shiga (1898). It is a short rod-shaped organism, with rounded ends, somewhat resembling the typhoid bacillus, but non-motile. It can be cultivated on laboratory media, does not liquefy gelatine nor coagulate milk. It is decolorized by Gram's method. Other organisms have been described in epidemics of dysentery by different observers; and it is probable that the name dysentery is applied to conditions caused by various pathogenic agents. The *B. dysenteriæ* does not form soluble toxines in culture-media. It is agglutinated by the serum of convalescents from the disease, even in considerable dilutions.

The *B. dysenteriæ* has been found in many cases of **infantile enteritis**, and is probably one of the causes of this condition.

Yellow Fever.—Sanarelli (1897) isolated a bacillus from cases of yellow fever, which he considered to be the causal agent, and to which he gave the name of *B. icteroides*. It is not, however, now generally believed to be the true cause of yellow fever, in which infection is almost certainly conveyed by mosquitoes—a fact which suggests a protozoan organism as the infective agent.

III. Spirilla.—Two diseases, relapsing fever and cholera, are associated with curved organisms.

FIG. 183.



Spirilla of relapsing fever with red corpuscles. × 1000.

Relapsing Fever.—The *Spirochæta Obermeieri* (Fig. 183), often called "spirillum," is found in the blood in this disease. It was discovered by Obermeier in 1873. It is a zigzag, sharply curved, uniform thread, 16 to 40 μ long, with quick undulating movements. No spores are known. The organism takes the ordinary stains feebly, and does not retain the stain when treated by Gram's method. The organisms appear in the blood just before the commencement of an attack, and disappear with remarkable speed during the crisis. Metschnikoff states that during the apyrexial interval they accumulate in the spleen, where they are taken up by the multinucleated leucocytes. Soudakewitch has shown that the previous removal of the spleen enormously increases the mortality. Nothing is seen of the spirilla till the relapse, when they return. All attempts to cultivate them have hitherto failed. The disease has been inoculated from man to man, and from man to apes (Carter, Koch). It is said that the blood is not infective during the fever-free period, but that the splenic pulp is then infective. The blood of convalescents has an agglutinative action on spirilla, and contains a body (copula or opsonin) capable of effecting the destruction of the organisms in the presence of leucocytes. Schaudinn believes that the *Spirilla of Obermeier are immature forms of a parasitic trypanosome.*

Cholera.—Cholera has long been regarded as an infective disease, but nothing definite was known until 1883, when Koch began his work in Egypt and India. He found that in the most acute cases the intestinal mucosa was simply opaque with slightly swollen follicles, that the intestinal contents were like gruel, and that these contents consisted of an almost pure cultivation of the parasite presently to be described. In cases of somewhat longer duration, he found the follicles and Peyer's patches surrounded by zones of hyperæmia, running together into red areas; and, in the least acute cases, the small intestine became intensely congested, the congestion being most marked above the ileo-cæcal valve and dying away in the upward direction. In these cases the intestinal contents became increasingly blood-stained, and finally exhaled a distinctly putrefactive odor, whilst the parasite above referred to was more or less replaced by other bacterial forms.

In the stage of patchy redness, sections of the mucosa parallel to its surface showed that, in the most acute cases, the redness corresponded to an invasion of the epithelium of the tubular glands by the parasite found in the intestine: the organisms were found lying between the epithelium and the basement-membrane. This bacterium, therefore, soon attracted attention by its definite form and by its apparent constancy.

Koch's cholera-spirillum or *vibrio* is about one-half to two-thirds the length of a tubercle-bacillus, but thicker (about 0.5 μ). It is curved, usually to a degree equal to that of a comma—hence the first name, *comma-bacillus*—but sometimes to that of a semicircle. It multiplies by transverse division, and, when the organism is grown upon gelatinous

Fig. 184.

Cholera spirilla. Flagella not shown. × 1000.

media or the intestinal mucosa, the segments separate from each other at once; if two remain united, they form an S-shaped figure (Fig. 184), their curves being in opposite directions. When cultivated for any length of time in nutritive fluids, the spirilla may remain united until they form delicate spirals of some length, very like the spirilla of relapsing fever: these are probably degenerative forms. A single flagellum is usually attached to one end of each organism. Occasionally two or more flagella may be similarly attached. More rarely still, flagella may be connected with both ends. Both single cells and spirals are actively motile. When present in the intestines in large numbers they form, according to Koch, little heaps in which the single cells have all the same direction; so that it looks as if a little swarm of them were making their way one behind the other, like fish in a slowly moving water (Fig. 184). The organisms stain with the ordinary solutions before mentioned, but do not retain the color when treated by Gram's method. Other organisms possessing the same anatomical characters have been described by several observers. Gruber

maintains that in the cholera-spirilla variations in the size, curve, sharpness of ends, and number of flagella are common, and depend on the special epidemic in question, on the conditions of growth, and on the age of culture.

FIG. 185.

Cholera-vibrio. Stab-culture in nutrient gelatine.

Culture-experiments show that the vibrio grows well upon all the ordinary media, and its exceptionally rapid multiplication can be watched in a drop of meat-infusion upon the under surface of a cover-glass. If linen, stained with cholera-dejecta, be kept moist and exposed to the air, growth is also very free for two or three days. The colonies upon nutrient gelatine or agar begin as very pale tiny spots, which, as they get larger, present a slightly irregular outline and a finely granular surface. Koch compares them to heaps of powdered glass. On the second day the gelatine liquefies in the immediate neighborhood of each point, and the colony sinks into a bell-shaped depression with a white apical point. The appearance of a long narrow funnel is very typical when a tube is inoculated by puncture. In the case of allied organisms, liquefaction generally takes place more rapidly. The proof of the individuality of this organism depends upon the combined evidence afforded by (1) the microscopic appearances; (2) the results of cultivation on gelatine and on agar; (3) the indol reaction with peptone-cultures; and (4) the effects of inoculation on animals.

The growth reaches its limit in a few days, remains a short time stationary, and then diminishes, the bacilli either shrivelling or swelling, and staining more or less imperfectly. Many strange "involution-forms" appear: these have been thought to belong to different species. Clear spots failing to stain have been regarded as spores; but spirilla containing these spots are not more resistant than others, and it is now generally acknowledged that no spores are formed.

Growth is most rapid at 86° F. to 104° F., and stops if the temperature falls below 60.8° F. Death results from exposure to a moist temperature of 131° F. (55° C.). Oxygen is essential to *growth*, but neither its absence nor an atmosphere of carbon dioxide causes death. An alkaline reaction is most favorable to growth, while distinct acidity often arrests it; but all acids have not this effect, for though the surface of a potato is acid, yet growth occurs freely upon it. Koch added many antiseptics to cultures, in order to discover those which most powerfully hindered development. Quinine (1 : 5000) and mercuric chloride (1 : 100,000) head the list, but it is obvious that the constitution of the material to which they are added will greatly affect the result. Koch's most important observation on this point was that *complete desiccation* killed the bacteria in three hours. It must be remembered that in pappy substances many hours may be required to complete

desiccation, but, even in such, twenty-four hours suffice to destroy cholera-germs. Cholera is, therefore, not often conveyed by the air, except through the medium of flies. Lastly, it is very probable, if not certain, that this spirillum soon dies in putrid fluid, cesspools, and the like, and that consequently the addition of antiseptics to such collections of matter may possibly preserve rather than destroy the cholera-germ.

Koch's *theory as to its action* is that, being confined to the intestine, it produces a virulent general poison, which is absorbed and at the same time acts as an intense irritant to the mucous membrane. Early death in collapse, perhaps before the passage of a single stool, may result from general poisoning, and it is in these cases that the intestine is found pale—simple hyperæmia having died away. In less acute cases the local effects become more marked, and increasing extravasation of red corpuscles remains to indicate the existence of the hyperæmia. Then the cholera-germ having reached the limit of its development, is more and more replaced by putrefactive germs, the products of which are extremely irritant and poisonous. Various toxic bodies have been obtained from cultures of the cholera-spirillum. These, when injected, give rise to cramps, cardiac failure, and lowered temperature, respectively. The exact nature of these is at present unknown.

Koch *failed to find the vibrio in any cases but those of cholera.* Metschnikoff has, however, pointed out that, during a neighboring epidemic of cholera, the drinking water of Versailles contained the cholera-vibrios, but that those who drank the water remained unaffected. He has further shown that the organism persisted in the water for months after the epidemic had ceased, and therefore that the appearance of the microbe in water did not necessarily involve the appearance of an epidemic. He believes that cholera-organisms may exist for some time in the intestines of animals without producing cholera. This result he attributed to the inimical action of the other organisms present.

The possibility of inoculating the disease must now be considered. By an accident, cholera-dejecta became mixed with water: this was drunk by seventeen persons; of these, five developed cholera. Again, at Berlin, during a course of demonstrations upon the bacteria of cholera, one of the members of the class was attacked by a distinct though mild form of the disease, his stools containing numbers of spirilla: no other source of infection could be ascertained.

In health the acid gastric juice rapidly kills cholera spirilla. Infection may, however, be produced in guinea-pigs and dogs by injecting the organisms into the duodenum; or by introducing them into the stomach if the gastric juice be first neutralized with sodium carbonate, and the peristalsis of the intestines paralyzed with opium to prevent premature expulsion of the organisms.

Infection through the stomach is probably much easier in man than in guinea-pigs. Ewald finds that water introduced into an empty stomach remains neutral, or even becomes slightly alkaline; its quan-

tity decreases slowly for an hour or more; then decreases suddenly—evidently from opening of the pylorus—before its reaction has become acid. Cholera-spirilla, introduced shortly before this occurrence, might reach the duodenum alive. As with other acute specific diseases, only a few of those persons exposed take the disease; and, according to Koch, almost all these are suffering from digestive troubles, gastro-intestinal catarrh, or an overloaded stomach—conditions diminishing the general acidity of the stomach and enabling the spirilla to escape with undigested masses.

The *contagion of cholera exists in the dejecta*, and quite exceptionally in vomit (when this has regurgitated from the intestines). For the disease to spread, moisture is essential—as desiccation as a rule means death of the organisms (see above). Cholera, therefore, does not, like tuberculosis, spread by the shaking of dust from linen; it is not carried by post nor by merchandise, but by man. As a rule, it is spread by the infection of water; this occurs very easily in India, where a large tank is employed to collect water for many people; and the one tank is used indifferently as a public bath, a wash-tub, a cesspool and a reservoir of drinking-water. In many instances, a supply of pure water has prevented the recurrence of the disease where previously it had been rife. Most provisions may be infected by contaminated hands or perhaps by flies.

It has already been shown that *this parasite can multiply apart from the body*,—*e. g.*, on moist linen, on potato, or in meat-infusion. As it requires rather concentrated nourishment, it probably does not multiply in ordinary running water; but many of the rivers of India are extremely foul, and organic matter increases greatly where the waters stagnate, drains and gutters enter, and vegetable and animal refuse collects; at such places the water may be turbid from germs. Stagnant surface-water, therefore, seems to be the great culture-ground for cholera-germs external to the body.

The serum of choleraic patients possesses agglutinative properties upon the spirilla similar to those described in the case of the bacillus of typhoid fever (p. 320), and the serum and peritoneal fluids of immunized animals are actively bactericidal toward them (see p. 293). For an account of preventive vaccination against cholera, see p. 237.

The belief that Koch's spirillum is the exciting cause of cholera depends on (1) its proved individuality (p. 330); (2) its constant presence in the intestines of persons suffering from the disease; (3) its absence from all other cases; (4) the accidental infection of persons working with it; (5) the protective power of Haffkine's vaccination; (6) the agglutinative properties of the serum of cholera-patients; and (7) the correspondence between the law of its growth and the conditions known to exist in cholera-epidemics.

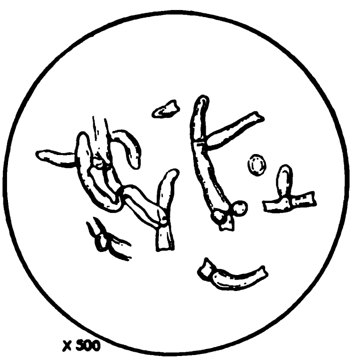
The Blastomycetes or Yeasts.

These are small, round or oval cells, which multiply by budding (*gemmation*). Sometimes the cells cohere and form branching chains. In some varieties, when food is not abundant, as in the case of potato-cultivations, one to four spores may form in the interior of the yeast-cells; in others no spore-formation occurs. On this basis the blastomycetes are divided into two groups: (1) the *Saccharomycetes* or true yeasts, which form spores, and (2) the *Torulæ*, which do not. The spores develop when placed in fermentable fluids. At other times under unfavorable conditions unjointed mycelium may be produced. When it is remembered that the growth of some higher fungi (*e. g.*, Mucor mucedo) under *exceptional* circumstances is the same as that of yeasts under *ordinary* circumstances—*i. e.*, by gemmation, it seems possible that yeasts may really be vegetable forms of higher fungi.

Yeasts are of importance chiefly as causes of fermentation. Recently, fungi referred to this group have been isolated from certain tumors and claimed as the cause of these formations (p. 97). Certain blastomycetes also give rise to a form of dermatitis. Torulæ are common in the stomach either alone or in company with sarcinæ. They are frequently found in diabetic urine, but not at the time it is passed, being deposited from the air and growing readily in the saccharine fluid.

Thrush.—In this disease, pale gray patches adherent to the mucous

FIG. 186.



Oidium albicans. Cells and spores seen on the surface of epithelium, scraped from an "aphthous" patch on an infant's tongue. × 500.

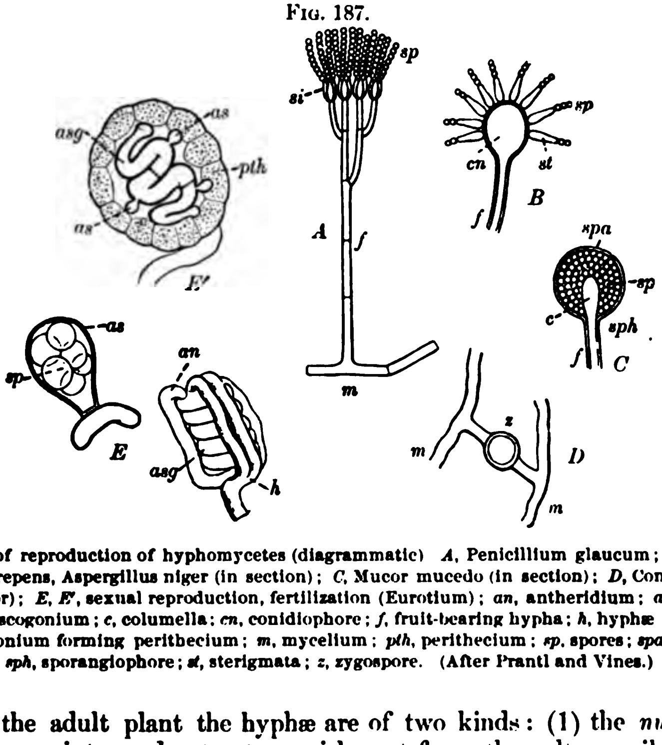
membrane form in the mouth, pharynx, and gullet, either of children at the breast or of adults exhausted by wasting diseases (*e. g.*, typhoid fever, phthisis). These patches are due to the growth of the **oidium albicans**, a parasite of which the botanical position is doubtful. It is generally regarded as a mould; but Grawitz states that, when cultivated, this fungus shows itself to be a yeast, and probably the *Mycoderma vini*, which he has proved capable of growing on mucous membranes. The patches consist of tortuous, often branched fila-

ments, formed of long cells united end to end and distinctly constricted where they join. The filaments end in rounded cells, which produce one or more spores: these form heaps in the epithelium (Fig. 186).

The Hyphomycetes or Moulds.

These consist of filaments (*hyphæ*) formed by a single row of cells placed end to end, growing by means of an apical cell which elongates and divides transversely. Lateral offshoots are common, but dichotomous branching is rare. Hyphæ may occur singly, but usually they are numerous, intertwining loosely or closely so as to form a feltwork (*mycelium*). All spring from an axis or *germinal tube* which grows directly from a germinating spore. Their growth is extremely slow compared with that of bacteria (p. 268).

FIG. 187.



Methods of reproduction of hyphomycetes (diagrammatic) *A*, Penicillium glaucum; *B*, Eurotium repens, Aspergillus niger (in section); *C*, Mucor mucedo (in section); *D*, Conjugation (Mucor); *E*, *E'*, sexual reproduction, fertilization (Eurotium); *an*, antheridium; *as*, ascus; *asg*, ascogonium; *c*, columella; *cn*, conidiophore; *f*, fruit-bearing hypha; *h*, hyphæ covering ascogonium forming perithecium; *m*, mycelium; *pth*, perithecium; *sp*, spores; *spa*, sporangium; *sph*, sporangiophore; *st*, sterigmata; *z*, zygospore. (After Prantl and Vines.)

In the adult plant the hyphæ are of two kinds: (1) the *nutritive*, which grow into, and extract nourishment from, the culture-soil, forming the mycelium; and (2) the *reproductive*, which spring from the mycelium, and stand up from the substance in which it lies: these are called aërial or fruit hyphæ. They are simple or branched, and bear at their ends spores or sexual organs. Reproduction is either asexual or sexual; the two methods may occur together on the same plant, or may alternate regularly or irregularly. In either case spores are formed—

round, oval, or cylindrical, smooth or irregular, colored or colorless: most are motionless, but some "swarm." Each consists of a little mass of protoplasm, surrounded by an envelope, which is made up of an outer (*exosporium*) and an inner (*endosporium*) layer: the exosporium is often pigmented. All spores have great power of resisting the action of physical and chemical agencies, and retain life for long periods; those formed asexually are ready at once to germinate, but those due to a sexual process almost always require a rest. The latter are the true *resting-spores;* but this name is often applied to all spores capable of retaining life for long periods in spite of adverse conditions.

To understand the above and what follows, the student should examine a few moulds from the surface of thin jam, paste, decaying fruit, or the surface of a slice of potato which has been exposed for an hour or two in a dwelling-room. In all, the aërial portion is easily studied, and the mycelium is readily shown by crushing a bit of the culture-ground under a cover-glass.

Asexual spore-formation occurs in three ways (Fig. 187):

(1) Hyphæ spring from the mycelium, and perhaps branch. The terminal cells divide transversely into spores (*conidia*), which either fall away singly or form chains.

(2) A hypha (*sporangiophore*) stands up from the mycelium, and its end swells into a ball (*sporangium*) full of protoplasm, which segments and forms conidia.

(3) From the surface of a knob on the end of a hypha (*conidiophore*), peg-like processes (*sterigmata*) sprout, each sterigma, by growth and transverse division, forming a chain of spores.

Sexual reproduction occurs in the following ways:

(1) *Conjugation.*—The apical cells of two hyphæ meet end to end and blend into one cell (*zygospore*). From this, after a longer or shorter rest, a sporangiophore sprouts, and from its spores new plants grow, as in Mucor.

(2) *Fertilization.*—The end of a hypha becomes twisted like a cork-screw, more and more closely, until the turns form a continuous tube—the *ascogonium*. From the lower turns spring fine branches, one of which (*antheridium*) conjugates by its apex with the ascogonium; the others simply cover the ascogonium continuously, and are converted by division into polygonal cells, which form a capsule (*perithecium*) round it. Many transverse septa form in the tube of the ascogonium, and from the cells thus produced flask-shaped lateral projections (*asci*) develop: in each of these, eight spores generally appear. The perithecium thins as the asci enlarge, the walls of the asci disappear, and an easily ruptured sphere of spores remains. When these germinate the endospore swells, splits the exospore, and throws out the germinal tube, whence springs the mycelium.

Conditions of Life. *Food.*—Possessed of no chlorophyll, moulds are unable to build up carbon-compounds. They assimilate those built up by other plants or animals. They are therefore always either

saprophytes or parasites: in the latter case they may kill their host. They require a free supply of oxygen; but some can obtain it, at least for a time, by decomposition of organic compounds like sugar. Thus, *Mucor racemosus*, cultivated on the surface of a saccharine liquid, absorbs oxygen, oxidizes some of the sugar, forming carbon dioxide, and grows rapidly. If deprived of oxygen, as by immersion, only the mycelium grows, and this becomes broken up into short cells, which multiply by budding, and much resemble yeast-cells. The growth is then much slower, carbon dioxide escapes in bubbles, and alcohol appears in the liquid. These changes soon cease, and the process can only be started again by a fresh supply of oxygen (Duclaux). Some moulds, such as *Penicillium glaucum*, and *Aspergillus niger*, have no power of thus obtaining oxygen, and die if cut off from the free gas. The change in the character of growth above mentioned, accompanying changes in conditions of life, has been pointed to as evidence in favor of the mutability of bacteria.

Light.—Many moulds can develop completely without light: some require it for the formation of spores and other processes.

Temperature.—Ziegler states that moulds flourish best at temperatures *below* that of the body, and that some will not grow at all at so high a temperature. A few species of aspergillus and mucor grow well between 95° and 105° F. The spores are as resistant to external agencies as are those of bacteria.

Water, or at least dampness, is essential for the growth of moulds.

Moulds are associated with processes of *rotting* or *decay*. The peculiar smell and taste which they impart is well known. The products of their life-action have not been closely investigated, but they are neither very poisonous nor very irritating, so far as *human* tissues are concerned.

Distribution.—The spores of moulds are much more numerous in the air than are other organisms. They, therefore, constantly fall upon the skin and enter the air-passages with air and the food-passages with food. As a rule, they find no nidus suitable for their development: the supply of free oxygen is often insufficient, and the temperature too high. Certain of them, however, when brought into contact with accumulated inflammatory discharges, or with sloughs, take root and fructify. This is most likely to occur in the nose, mouth, and pharynx. They are here saprophytes, but the products to which they give rise may irritate the living tissues lying beneath the parts in which they grow. Species of mucor and aspergillus are those commonly found under these conditions.

Pathogenic Moulds.—Owing to the peculiarities mentioned in their life-history, these fungi have but little power of invading living tissues. Certain skin-diseases are, however, due to the growth of species of this class in epidermic structures: they are (1) *Favus*; (2) *Tinea tonsurans*, *T. kerion*, *T. circinata*, *T. sycosis*, *T. unguium*; (3) *Tinea versicolor*, and (4) *Erythrasma*. The fungi causing the diseases actinomycosis and mycetoma or Madura foot have been sometimes assigned to this class.

Their exact position is still undecided, but they are generally regarded as forms of streptothrix. Instances of the invasion of living tissues by varieties of *aspergillus* (*A. fumigatus*, *A. niger*) are occasionally met with. Thus by the growth of the fungus in the lungs a disease is produced somewhat resembling tuberculosis in its symptoms (*pneumomycosis* or *aspergillosis*). A form of *mucor* has been described as giving rise to a dermatitis closely resembling scabies (Luck): the same fungus was also found in a case of intestinal ulceration complicated by cerebral abscess (Paltauf).

Favus.—The *Achorion Schönleinii* forms almost the whole of the light yellow, mouldy-smelling crusts characteristic of favus. On hairy parts—the usual seats of the disease—the hairs are always invaded, especially the roots. Here the parasite grows luxuriantly, but it does not extend far up the shaft; its primary seat is the epithelium of the hair-follicle. On other parts the mycelium invades the *deeper layers* of the *epidermis*, and may even penetrate to the corium: in this case the local irritation will be more marked. The mycelium consists of unjointed, branching, confusedly intercrossing tubes; in certain of them, which become divided into joints, oval spores form.

The nails are very rarely invaded, and then only by mycelium.

Tinea Tonsurans.—The *Trichophyton tonsurans* [1] is generally assumed to be the one parasite common to Tinea tonsurans, Tinea kerion, Tinea circinata, Tinea sycosis, and Tinea unguium. Different varieties have been described. These are distinguished by the size of the spores (*T. megalosporon*, *T. microsporon*), their position, either within the hair-shaft (*endothrix*) or outside it (*ectothrix*) and their culture-results (Sabouraud). These forms are not found growing together.

When the hair is affected, the root and the lower part of the shaft are crammed with spores, lying in rows between the fibrils of the degenerated hairs, which are opaque and brittle (Fig. 188). It is doubtful

FIG. 188.

Hair-shaft infected with Trichophyton tonsurans. Showing mycelium and spores on surface and in substance of hair-shaft. × 250.

how far the fungus makes its way down between the shaft and the wall of the follicle before it penetrates the former. The hair breaks just beyond the scalp, leaving a stubbly line of split or twisted ends. Epidermic scales from the surface of the scalp may contain the fungus, but

[1] Greek θρίξ, a hair; φυτόν, a plant.

the deeper living cells of the root-sheaths are always free from it (Thin and Taylor). Spores are abundant, and oval in shape; mycelial threads are rare. Points worth remembering in connection with the undoubted fungoid origin of the disease are (1) its usual limitation to children; (2) its tendency to fasten upon the weakly; (3) its great contagiousness when acute, diminishing as it becomes chronic; and (4) its greater severity when contracted from animals, as the horse (*Trichophyton megalosporon*). It may excite severe irritation and even suppuration—**T. kerion.**

Tinea circinata.—Here the parasite infests epidermic cells, always causing desquamation, sometimes vesiculation, or even more severe inflammation. It spreads uniformly from the point at which it first takes root, and consequently assumes the form of a gradually enlarging circle. The central parts of the fungus die, and the growing edge produces a ring of hyperæmia in its neighborhood. Mycelium is present chiefly in the form of very long, jointed and branched threads; the spores are scanty, single, or in short chains. The fungus altogether is often scanty, and is especially difficult to detect if it has excited inflammation.

Tinea sycosis. (*Trich. megalosporon.*)—When attacking the beard, the fungus is found chiefly in the hair, but also in the follicle; both mycelium and spores are seen, the latter in excess, but not so markedly as in T. tonsurans. The mycelium generally lies round the root of the hair, and is pulled out of the sheath with it. Severe inflammation is generally excited.

Tinea unguium.—Mycelial threads of trichophyton may occasionally invade a finger-nail, rendering it opaque, thick, and brittle. Unlike the effects of a general disease, these changes occur in two or three nails only, and the toe-nails are scarcely ever affected. In this situation it is extremely difficult to destroy.

Chloasma, Pityriasis versicolor.—The *Microsporon furfur* invades the horny layer of the epidermis of covered parts of the trunk, growing more superficially than any of the above, rarely causing irritation and not attacking nails or hair. It consists of jointed mycelial threads, which are always abundant; and spores, which vary in form, lie in groups and grow at the ends of the mycelial threads. On the skin it produces patches of brown discoloration.

Erythrasma is a rare disease, due to the growth of the *Microsporon minutissimum.*

CHAPTER X.

CERTAIN INFECTIVE DISEASES.

SEPTICÆMIA AND PYÆMIA.

THE diseases known as *Sapræmia*, *Septicæmia*, and *Pyæmia* result from the absorption and dissemination throughout the body of organisms—mainly pyogenic cocci—and their products.

Under *Sapræmia* (*Septic Intoxication*) are included those forms of septic absorption which are due to the introduction of the chemical products of the organisms without the organisms themselves; and under *Septicæmia* (*Septic Infection*) those forms due to the introduction and multiplication of the organisms within the body. Neither of these diseases is accompanied by secondary suppuration. *Pyæmia*, on the other hand, is a term used to denote those cases of septic infection which are characterized by the presence of septic embolism and abscesses. The three conditions are frequently associated. These maladies were formerly the chief causes of the mortality in large surgical hospitals, and the overcrowding of patients with septic wounds was indirectly the cause of these diseases. Almost every case was due to the infection of a previously existing wound with organisms conveyed by fingers, instruments, dressings, or air.

1. **Sapræmia.**—The constitutional effects produced by the absorption of pathogenic organisms are always due to the toxic effects of their products. It is theoretically conceivable (1) that in some cases these products may be absorbed without any of the organisms which gave rise to them; and (2) that, even if any organisms be simultaneously introduced, they may be accompanied by so large a quantity of the poisonous products that death will follow before the organisms have time to multiply and afford proof of their presence. In both these instances symptoms will rapidly follow infection—as in any other case of chemical poisoning. In the former cases the disease will be non-infective, that is, the inoculation of another person with small quantities of the fluids from the body of an individual suffering from the disease (sapræmia) will fail to produce the condition, for infection depends upon the presence of living organisms which multiply in the body of the person inoculated, whereas the toxic products themselves have no power of self-multiplication. If, in the second instance, the patient survive the immediate effect of the *sapræmia*, the organisms simultaneously introduced may develop and their products give rise to less acute but gradually increasing effects, precisely similar to those resulting from the introduction into the body of a number of septic organisms without any large quantity of their products (*septicæmia*). In

this case the organisms, the source of the poison, will multiply and become so generally distributed that a single drop of blood may suffice to inoculate another patient with the disease.

The word sapræmia[1] literally means the entrance of *putrefactive* products into the blood-stream. Such products are poisonous, but they are only exceptionally formed within the body, as in instances of decomposition of pleural effusions, owing to admission of putrefactive organisms from without. Sapræmia is generally due to poisoning with the toxines of pyogenic cocci, which have developed in blood-clot or other discharges connected with wounds. This form of specific poisoning can occur only where extensive surfaces are open to the absorption of large quantities of septic products under considerable pressure. Such conditions may exist in bad compound fractures, in wounds of large joints or of serous cavities, and in the uterus immediately after parturition. Any of these may form an extensive culture-ground for organisms, the products of which may be rapidly absorbed. It is worthy of note that absorption takes place with comparative difficulty from a granulating surface; hence septic intoxication is commoner as an immediate result of an operation or injury than at later stages, when granulation-tissue has had time to form. Pure *sapræmia* without any *septicæmia* is rare.

Diphtheria and tetanus are also instances of sapræmic diseases, inasmuch as the bacilli in both instances remain localized, and do not, apart from exceptional cases, enter the blood-stream.

2. **Septicæmia.**—All diseases in which living organisms multiply in the blood-stream are technically instances of septicæmia: examples are seen in plague and Malta fever. Practically the term is usually limited to cases of infection with pyogenic organisms, especially streptococci. Infection may occur from the smallest prick; no large wound is necessary. The organisms grow in the blood, and small numbers can be found when it is examined. Many adhere to the endothelium of the capillaries, and by their growth and "clumping" form plugs which block the vessels, in some cases giving rise to minute hemorrhages and occasionally to miliary abscesses. The factors which determine why in one case these organisms produce a local abscess and in another blood-poisoning have been already considered (p. 179). They depend principally upon the virulence of the organisms and the kind of chemotaxis to which they give rise; but in any case the symptoms are due to the chemical products of the organisms.

The blood in cases of septicæmia generally contains an increased number of leucocytes, while there is destruction of red corpuscles, to which the jaundice often seen in these cases has been attributed. The petechial hemorrhages that occur may be due to an action of the toxines upon the walls of the capillaries, similar to that which takes place in snake-poisoning (Chap. XII.). Fever of a remittent type is the usual accompaniment of the condition, and prostration and delirium are marked features. Living organisms may be cultivated from the blood, and often from the urine.

[1] Greek, σαπρός, putrid. The term "sepsis" as used in surgery is applied to invasion by pyogenic cocci, rather than to putrefaction.

The *post-mortem changes* in *Sapræmia* and *Septicæmia* are indefinite, but practically identical. Decomposition sets in early, owing to the organisms present. The lining membrane of vessels and heart is often blood-stained from the rapid disintegration of the red corpuscles. Minute hemorrhages may be found anywhere, especially beneath serous membranes; and the spleen is enlarged. The bases of the lungs are congested, partly because of the changes in the vessels and partly because of the heart-failure which precedes death.

3. **Pyæmia.**—Pyæmia differs from septicæmia in that the absorption and dissemination of the poison give rise not only to a general infective disease, but also to scattered abscesses. This is the distinctive pathological characteristic of the disease. It is always accompanied by some septicæmia.

The source of infection is usually some suppurating wound; but cases may arise independently of any wound, as seen in acute osteomyelitis, infective endocarditis, and those rare cases of "spontaneous" pyæmia in which no primary lesion can be found. In these cases the poison has probably entered through some trivial, unobserved lesion in the skin or mucous membrane. As in septicæmia, it gains access to, and is distributed by the blood. Any of the pyogenic organisms are capable of producing pyæmia, but the *Streptococcus pyogenes* is the one most frequently found (p. 307). Clinically the disease is generally signalized by an intermittent form of pyrexia, rigors often occurring with each rise of temperature. The other features are those of septicæmia.

The secondary abscesses are of two kinds: (1) those which follow embolism, and (2) those which occur without any apparent local cause.

(1) The *first* kind of abscess is due to septic embolism (p. 225). Suppurative phlebitis occurs in a vein connected with a septic wound. Thrombosis in the vein follows. The thrombus softens (p. 216), and the resulting fragments are carried on in the circulation. These become arrested in the pulmonary capillaries, or, if small enough, pass through them and are lodged in the kidney or spleen. Wherever these infective fragments are arrested, suppuration occurs. Thus, suppuration in the middle ear may produce, by direct extension, inflammation in the wall of the lateral sinus and consequent thrombosis. Fragments of the softened clot may be carried to distant parts, and give rise to ulcerative endocarditis, and abscesses in the lungs and kidneys.

Embolic abscesses, due to pyæmia, are most frequent in the *lungs*, but may be found in the liver, spleen, kidneys, and brain. They may occur in any vascular part. They lie generally upon the surface of organs immediately beneath the capsule. They vary in size from minute, scarcely visible, points of suppuration to cavities an inch or more in diameter; they are usually multiple and may be very numerous. They are surrounded by a hyperæmic zone. Often more than one organ is affected, and these abscesses may occur with others of the second kind. Sometimes the lungs escape, while other organs, lying beyond them on the blood-path, are affected.

Suppurative pylephlebitis or portal pyæmia is a local variety occurring as a rare complication of chronic ulceration in any part of the gastro-

intestinal tract, of suppuration of the gall-bladder, or in the neighborhood of the portal fissure, or of inflammation of the umbilical vein in newly-born infants. It gives rise to small multiple abscesses, often scattered throughout the liver, but always in connection with branches of the portal vein.

(2) The *second* kind of abscess is a diffuse suppuration occurring in the subcutaneous and intermuscular connective tissue, in the joints and in the serous membranes. In these cases the irritant is conveyed to the spot by the blood, and lodges there, either because the nidus is suitable, or because some capillary embolism has occurred. This form of suppuration may occur alone or be combined with the first variety.

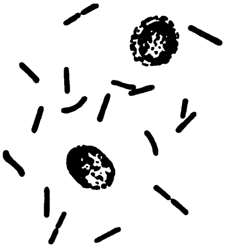
A disease somewhat similar to pyæmia has been produced in animals by the introduction of pyogenic cocci into the blood.

Besides the abscesses, the following *post-mortem changes* may be found. As in all septic diseases, rigor mortis is feeble and decomposition sets in early. Emaciation is generally marked, and the skin yellow or jaundiced. Petechiæ may be present. The wound, if there be one, is sloughy, offensive, and perhaps surrounded by diffuse inflammation. Thrombi are present in one or more inflamed veins leading from the focus of infection, and are undergoing infective puriform softening (see Phlebitis); the ends of one or more thrombi perhaps project into a large vein in which the circulation is not arrested. The blood is generally normal to the naked eye, but microscopically it contains an excess of leucocytes. Hypostatic congestion of the lungs is generally present, the spleen large and pulpy, and the heart, liver, and kidneys show cloudy swelling.

TUBERCULOSIS.

Tuberculosis is an infective disease due to the growth of the *Bacillus tuberculosis* in the tissues of the body. The characteristic naked-eye manifestation of the growth of this organism is the formation of small circumscribed inflammatory lesions known as "tubercles." When these are distributed throughout the body the disease produced runs a rapid course, and is known as *acute general tuberculosis;* when they are limited to a special organ or tissue the disease is of much longer duration, and is termed *local tuberculosis*—*e. g.*, *tuberculosis of the lungs* or *kidneys*. A local tuberculosis often serves as a point of origin for general infection (*acute general tuberculosis*).

FIG. 189.



Bacillus tuberculosis. × 1000.

Morphology of the Bacillus.—The bacillus is a minute organism, 2 μ to 6 μ long—two or three placed end to end being thus equal to the diameter of a red blood-corpuscle. It is very thin ($\frac{1}{5}$ to $\frac{1}{6}$ of its length), motionless, and rounded at the ends. It can be easily stained by the Ziehl-Neelsen (p. 301) or by Gram's method (p. 300). It has often a beaded appearance, clear spots alternating with stained parts

(Fig. 189). The bacilli are usually straight, but may be curved: in the large majority of cases they occur singly, but occasionally are found in pairs. Multiplication is very slow and takes place by fission.

The organisms can be cultivated on media containing glycerin or blood-serum and are aërobic. Their growth is slow, and it is only after some weeks that a culture presents its most characteristic appearance. By that time the colonies have to the naked eye a heaped-up, scaly appearance, the older parts looking dry and shrivelled (Fig. 191). When examined under the microscope the margins of the colonies show a peculiar wavy form, due to parallel chains of organisms following the same curve (Fig. 190). Under favorable circumstances cultures of tubercle bacilli exhibit a variety of different forms, branching threads being often seen. The bacillus is therefore pleomorphic, and is classed as a *streptothrix*. As the bacilli thrive only at a comparatively high temperature (82° F. to 108° F.), they do not *multiply* under natural conditions outside the body, but live a wholly parasitic life. They can, however, *exist* outside of the body for some weeks, and have even been found to retain their virulence after such existence for six weeks in putrid sputum, and for six months in the dry state. In putrid fluids they do not long hold their own against the rapidly multiplying septic organisms, which are better adapted for the ordinary conditions outside the body. Their virulence is very constant; nearly two years' cultivation failed to attenuate it (Koch). Other observers have, however, succeeded in producing attenuated strains. The bacilli are readily destroyed by boiling and by sunlight. Desiccation without sunlight does not destroy them. They resist the action of a 1 : 1000 solution of perchloride of mercury for some minutes. A 1 : 20 solution of carbolic acid acts more rapidly.

FIG. 190.

Tubercle-bacilli, from a colony on blood-serum, showing the wavy parallel lines. × 500. (After Koch.)

Tuberculosis occurs in other animals besides man, and some controversy has arisen as to the identity or diversity of the organisms at work. Koch maintains that the bacilli of human and bovine tuberculosis are distinct; the balance of opinion is, however, rather in favor of regarding them as identical, but modified by circumstances so as to differ in virulence. Warm-blooded laboratory animals may be immunized against the form of the bacillus which usually affects them, by inoculation with organisms derived from cold-blooded animals (tortoise, blindworm).

Products of the Bacillus.—Koch concentrated and filtered the products of the bacilli, and called the filtrate thus obtained *tuberculin*. When injected into infected animals this substance produces fever and a marked local inflammation in the neighborhood of the tuberculous foci; but when injected into animals free from tuberculosis it produces

no effect, save, in some cases, a slight and transient rise of body-temperature. The B. tuberculosis produces three classes of poisons: (1) *albumoses* or fever-producing substance, (2) a *crystalline fatty acid* (*necrotic acid*) producing necrosis of the tissues with which it is brought into contact, and (3) *other poisons*, concerning which little is known. It has been found that the intraperitoneal or intravenous injection of the dead bacilli will cause the formation of *tubercles* in those organs to which the dead organisms are carried.

FIG. 191.

Tubercle - bacillus. Surface-culture on glycerine-agar.

Sources of the Bacillus.—In every case of tubercular disease the bacilli are introduced from without, and are derived directly or indirectly from some previous case of the disease in man or animals. The two principal sources of bacilli are (1) *the sputum of persons with tuberculous lungs*, and (2) *the milk of cows with tuberculous udders.*

1. **Sputum.**—When it is remembered that about one-seventh of mankind die of pulmonary tuberculosis, and that, in the majority of cases, the patients, for weeks or months, expectorate large quantities of bacilli, without any precautions being taken against infection, it is clear that there is an ample supply. The bacilli, with small particles of mucus, expelled by coughing, may be inhaled directly by the healthy; but the sputum which dries upon handkerchiefs, bedding, garments, furniture, and the walls and floors of workshops and other rooms, thence to be detached as dust, appears to be the most fertile source of infection.

2. **Milk.**—When the disease of the udders is extreme tubercle-bacilli can be found in the milk; but when the disease is less marked its infective quality can only be shown by inoculation, and, less certainly, by feeding. Butter made from infected milk is itself infective. It is probable that direct infection from tuberculuos milk is very rare; Raw, however, believes that tuberculosis in children is generally due to infection with bovine bacilli.

Other sources of tubercle-bacilli exist, but they are rare:

3. The **fæces** and the **urine**, in cases of tuberculosis of the intestine and the genito-urinary tract respectively, and the discharges from **tuberculous abscesses and ulcers**, are infective.

4. Tubercle-bacilli may be occasionally conveyed in **tuberculous meat.** The muscles themselves are rarely involved, but infected glands may be left, or the meat during its removal may be smeared with tuberculous material. The surface of meat, however, is generally raised to a temperature over 100° C. in the process of cooking; and this source of infection is, therefore, practically confined to those cases in which glands are eaten, or in which raw meat is prescribed in the treatment of disease.

5. **Tuberculous parents** may infect their offspring during intra-uterine development. This possibility will be referred to under the next section.

Modes of Entry.—There are four possible ways in which tubercle-bacilli may enter the body: (1) *inhalation,* (2) *feeding,* (3) *inoculation,* and (4) *in utero from the mother.*

1. **Inhalation.**—The inhalation of tubercle-bacilli is the most frequent cause of the disease, especially in adults. This is shown by the frequency with which the lungs or the bronchial glands are alone involved; by the readiness with which animals can be similarly infected, and by the accidental death, in one case, from pulmonary tuberculosis, of an assistant engaged in such an experiment. It does not follow that all the tubercle-bacilli inhaled pass into the tissues. In ordinary respiration they are not carried beyond the smaller bronchi, where they may be deposited, and as they multiply but slowly many are expelled by ciliary action and coughing before they can seriously injure any spot and effect an entrance. In the deep inspiration through the open mouth which follows the expulsion of the reserve air in coughing, the bacilli may be carried almost to the infundibula, if not to the air-cells, while the existence of pleural adhesions, or of a badly formed thorax, by limiting the movements of the lung will lead to the retention of local secretions.

Having no power of locomotion, the bacilli must be carried through the mucous membrane like the particles of carbon in anthracosis. The leucocytes, reaching the surface, may there meet, enclose, and in many cases carry them back into the tissues. If the cells sicken while the bacilli survive, the latter may find themselves in some place where they can thrive, multiply, and produce their characteristic lesions. In catarrhal states many phagocytes reach the inflamed surface, and any bacilli that may be present are therefore more likely to be introduced into the tissues. Not infrequently the bacilli may lodge and multiply in the mucous membrane, and the disease commence as a local tubercular bronchitis. When introduced directly into the alveoli, they may multiply and affect the alveolar epithelium and walls chemically without first entering them.

In the same way in children, and less frequently in adults who, because of nasal obstruction or habit, breathe through the mouth, the bacilli may reach the cervical glands and distant organs through the mucous membrane of the mouth and fauces.

2. **Feeding.**—Tubercle-bacilli may also enter through the alimentary tract from infected food. Possibly, in some cases where they pass through the mucous membrane of mouth and fauces, as has just been stated, they may be derived from the food. In the large majority of cases, however, bacilli derived from food enter by the intestine.

It is often found, especially in children, that no lesion is produced by the bacilli at the point of entry, but that marked changes may occur in the lymphatic glands or in distant parts; it is also well known that marked local changes in the walls of the intestine are

more often due to secondary infection from swallowed sputum in the case of persons suffering from advanced pulmonary tuberculosis, than to primary infection from contaminated food. An explanation of these facts is afforded by experiments on animals, for it is found that if *virulent infective material,* containing large numbers of bacilli, is used, marked local lesions occur at the seat of invasion, but that if *less virulent material,* containing only small numbers of bacilli, is employed, the seat of invasion presents no local lesion, while the neighboring lymphatic glands may be largely infected, and the bacilli be carried thence to distant parts. Now it is quite certain that the swallowed sputum in most cases of advanced pulmonary tuberculosis will contain a far larger proportion of bacilli than infected food, and the presence, or absence, of local changes at the seat of invasion seems, therefore, to depend upon the virulence of the infecting material.

There is some difference of opinion as to the principal seat of invasion in instances of tuberculosis occurring in young children. It is often stated that the lungs are not affected in the same proportion as they are in later life; that the disease is not so localized, general miliary tuberculosis being common; that the bones are frequently the seat of the disease; and that the lymphatic glands are more universally affected. It is also maintained that the intestine is the part most often attacked primarily, even in those cases in which the patients ultimately succumb from disease of the lung. It is certainly sometimes possible to trace the infection from an old calcified gland in the mesentery to the retroperitoneal, posterior mediastinal, and bronchial glands, and thence to the lungs. On the other hand, observers generally agree that, in the large majority of cases of tuberculosis in children, the bronchial or cervical glands alone are caseous—an indication that infection has occurred by inhalation, or through the mucous membrane of the mouth. Virulent tubercle bacilli have been found under the nails of children, being probably picked up in the act of crawling on the floor. From the nails they may be conveyed to the mouth and cause infection.

3. **Inoculation.**—It occasionally happens that a wound, in an otherwise healthy person, becomes inoculated with tubercle-bacilli. Nurses have been thus infected by broken vessels containing tuberculous sputum; and persons taking part in autopsies on cases of tuberculosis, or wearing the ornaments of phthisical relatives, have also contracted the disease by the introduction of tuberculous material. In such cases the organisms may produce catarrhal inflammations of the skin; or they may cause delay in the natural healing of the wound, and, later on, give rise to progressive infection of lymphatics, glands, and distant parts. Sometimes, as in the case of the lungs and alimentary tract, the bacilli may cause changes in the glands and distant parts without producing any visible lesion at the point of entry.

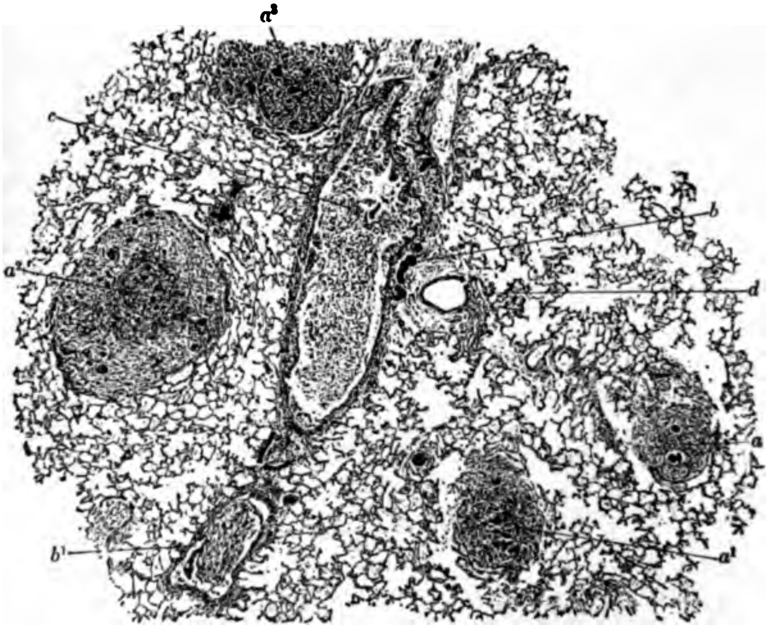
The majority of the cases of tuberculosis due to inoculation occur secondarily in cases of pulmonary tuberculosis, and are thus comparable to the intestinal tuberculosis which results from swallowed sputum.

Thus, the patient may inoculate an excoriation on the hand from an infected handkerchief or pocket.

4. Infection in Utero.—This may occur in cases of tuberculosis of the placenta. The possibility of latent tubercular disease being conveyed through the medium of the ovum or of the spermatozoa will be referred to when the influence of heredity is considered. (See page 357.)

Effects of the Bacillus in the Tissues.—Once deposited in the tissues, the bacillus proceeds to multiply, and to produce a special lesion which for a long time was considered characteristic, and is known as a **tubercle** (Fig. 192). Each tubercle, as a rule, contains the following elements : (1) centrally, either one or more multinucleated *giant-cells,* containing tubercle-bacilli (Figs. 193 and 194), or some granular

FIG. 192.



Acute tuberculosis of lung. a, a^1, a^2, a^3, recent tubercles, each made up of several giant-cell systems, in which the giant-cells are more deeply stained. In the centre of a^3 marked caseation has occurred; b, b^1, small bronchial tubes, at one point ulcerated and dilated, with engorged vessels (b); c, contents of bronchial tube : these consist principally of desquamated epithelium and leucocytes ; d, small branch of pulmonary artery. × 20.

débris surrounded by giant-cells ; (2) outside the giant-cells, in most cases, large cells with big nuclei and granular protoplasm, called *epithelioid cells* (fibroblasts) ; and (3) outside these again, a zone of *leucocytes,* which has no definite external or internal limit. The giant-cells in slowly developing lesions often send off processes which anastomose and help to form an open network in the periphery (Fig. 195). In the meshes of this reticulum the epithelioid cells and leucocytes lie.

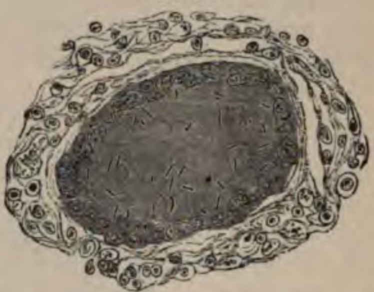
In other cases the reticulum is less prominent, and, according to many observers, is not infrequently absent.

A *non-vascular* nodule of the above structure is the anatomical characteristic of tuberculosis, but it is not microscopically distinguishable from the products of other very local chronic inflammations.

Fig. 193.

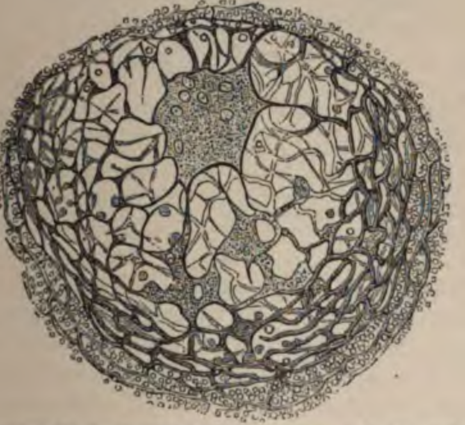
A caseating multinucleated cell from the lung in a case of chronic phthisis. Showing large number of nuclei, many of which are very indistinct. No bacilli are shown. × 600.

Fig. 194.



Tubercle-bacilli in giant-cell. From tuberculosis of horse. × 600. (Cheyne.)

Fig. 195.



Multinucleated and branched cells from a firm gray miliary tubercle of the lung in a case of acute tuberculosis. Wide meshes are seen in the immediate vicinity of the cells enclosing a few leucocytes. The branched processes are directly continuous with the reticulum of the tubercle. × 200.

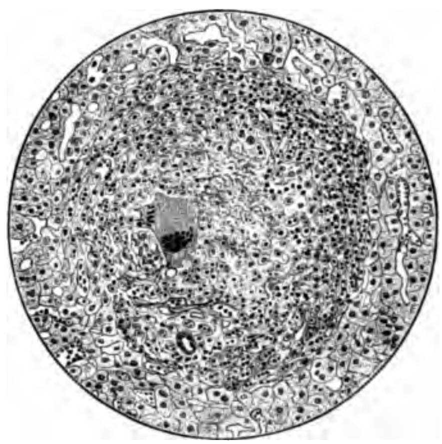
Baumgarten produced typical "tubercles" in a rabbit's cornea, by sticking fine hairs into it. Laulanie states that, in the lung-disease caused in dogs by the *Strongylus vasorum*, the ova and embryos may be seen in giant-cells surrounded by zones of epithelioid cells and leucocytes. In actinomycosis in animals an exactly similar arrangement of

cells is found round about the central *actinomyces* or fungus of the disease. More recently Flexner has described similar lesions produced in man by a form of streptothrix, and so-called *pseudo-tuberculosis* in rodents has been traced by A. Pfeiffer to a short thick bacillus differing in its characters from the tubercle-bacillus.

Nor can the above structure be said to be constant; for, especially in acute cases, some of the tubercles seem to consist entirely of small round cells—no epithelioid or giant-cells being visible. In the lung the alveolar epithelium often enters largely into the constitution of the lesions.

Each of the smallest tubercles visible to the naked eye consists of a group of three or four giant-cell systems of the above structure (Fig. 196). Foci thus formed are known as **gray, or miliary tubercles**

FIG. 196.



A giant-cell system, invisible to the naked eye, from the liver of a child, aged five, who died from acute tuberculosis. A giant-cell with two groups of nuclei and several bacilli is seen near the centre. Surrounding it is an area of commencing caseation in which the cells are becoming indistinct. Enveloping this is a zone consisting of epithelioid cells (fibroblasts) and leucocytes. The leucocytes are most numerous on the side where the caseation is most advanced. The whole mass is imbedded among granular liver-cells in the interlobular area. × 250.

(*gray granulations*, Fig. 192). They are grayish, semi-translucent, rounded bodies, varying from just visible points to nodules the size of a pin's head, or larger. They are firm and shot-like, distinctly circumscribed and prominent above the surface of the section. The term "**yellow tubercles**" is applied to foci which are rather larger, less regular, less closely defined, and softer than those just described. They may even form masses the size of a cherry or small walnut. In some cases most of the tubercles present are gray, whilst in others all are yellow; but it is frequently possible, in a single organ, to find tubercles showing the different stages in the formation of a yellow from a gray nodule. Caseation, commencing centrally, is the main cause of the difference between them. A large mass of yellow tubercle is formed, not by the continued growth of a single gray tubercle, but by the

blending of several arising close together and by the caseation of the participating gray tubercles and of the intervening inflamed tissue. It is often possible to recognize, round a yellow caseous mass, a narrow gelatinous zone, consisting of gray tubercles. Gray tubercles may also be seen radiating from the caseous focus into the surrounding tissues, thus indicating that infection from the central focus leads to the formation in its immediate neighborhood of fresh tubercles which, as they enlarge and degenerate, become part of the central mass. A yellow mass thus formed is called *conglomerate tubercle.*

Sometimes, especially in the lungs, the formation of giant-cell systems is followed by more or less acute inflammation in the surrounding tissues. This may be so great as largely to mask the tubercles themselves.

Source of the Cells in Tubercles.—Baumgarten's conclusions are now generally accepted. According to these, *the giant-cells and epithelioid cells are derived from the local tissue-cells,* including both epithelial and connective tissue. Baumgarten, experimenting with albino rabbits, introduced pure cultures of tubercle-bacilli into the anterior chamber of the eye. In a few days mitotic changes appeared in the connective tissue and endothelial cells of the iris. These changes were limited to the cells in which bacilli were present. They were followed by proliferation of the cells themselves, which gradually assumed an epithelioid type. The proliferating patch was then gradually invaded by leucocytes, until they quite obscured the epithelioid cells. Giant-cells were occasionally present, but only in the later stages; when present, they showed no sign of division but only of degeneration.

Metschnikoff, on the contrary, maintains that the cells believed by Baumgarten to be the progeny of connective tissue are uninuclear leucocytes. In the case of the lung he admits that the endothelial cells of the bloodvessels take a share in the process, and also attributes to them a phagocytic function. In his opinion a tubercle is formed by the *accumulation* of phagocytes and *not* by the *proliferation* of any form of cell. Giant-cells, according to his view, are phagocytes that have combined for the common weal; while to Baumgarten and Koch they are single epithelioid cells that have begun to multiply, but, though their nuclei have divided and their size has increased, have failed at the final stage of cell-division. In parts in which epithelium is present, as in the lung, liver, kidney, or testicle, there can be no question but that the epithelial cells multiply freely. In a lung affected by acute miliary tuberculosis many of the nodules do not contain the giant-cell systems above described, but consist of collections of epithelial cells in the alveoli. Giant and epithelioid cells, formed apparently from alveolar epithelium, are sometimes present.

The *giant cells* in tuberculosis usually have their nuclei arranged round the periphery: it has been suggested that the outer zone of the cell is the part which is best nourished, and that the nuclei lie there for this reason. The central part of a giant-cell is often necrotic. Giant cells in myeloid sarcoma have their nuclei distributed evenly throughout their protoplasm.

Secondary Changes in Tubercles.—The cells forming a tubercle invariably undergo further changes. The principal of these are (1) *fatty degeneration* and *caseation*, (2) *fibrosis*, (3) *calcification*, and (4) *softening*.

1. **Fatty Degeneration and Caseation.**—These changes are invariable. They commence in the centre of the nodule, the multinuclear leucocytes being the first to succumb. The epithelioid cells degenerate later. The central portion of a tubercle, in which caseation is commencing, consists of finely granular amorphous débris, containing, toward its periphery, shrunken nuclei—the relics of its original cells; not infrequently a more or less degenerate giant-cell, containing tubercle-bacilli, may be seen within the margin of the caseated area or in its immediate neighborhood (Fig. 196). The process of caseation varies much in rapidity. It is usually most marked in the larger and more diffused lesions, and these are, therefore, as a rule, of a yellow color and soft consistence.

2. **Fibrosis.**—In other cases the retrograde change may be less marked. The central portion undergoes fatty degeneration and is more or less completely absorbed, whilst the cells at the periphery are gradually replaced by a dense, contracting, fibrous capsule. Ultimately a mere scar may remain, but small caseous areas are frequently present in the midst of the fibrous tissue.

It will be noticed that this "fibroid change" is simply the encapsulation of a slightly irritant foreign body, and occurs as readily round a bullet or piece of wire lying in the tissues as round tubercular organisms in fatty detritus. In both cases it must be regarded as an attempt at repair. This replacement of the tuberculous tissue by scar-tissue occurs in the smaller lesions and in many of larger size which open upon the inner or outer surface of the body, and from which the infective material can be thus discharged. The change obviously tends to protect the organism against general infection from the focus in which it occurs, and indicates that the tissues have gained the upper hand and have imprisoned the bacilli. When complete it is the most favorable change that can possibly occur.

Sometimes, especially in cases which have run a chronic course, and in which the diagnosis may have been "chronic bronchitis," hard, glassy bodies, often specked with black pigment, are found in the lung-tissue. There is no caseation, and the microscope shows the masses to consist of almost hyaline fibrous tissue. This complete fibroid transformation is said to occur occasionally in lymphatic glands, and indicates that the bacilli are dead. On the other hand, while the caseated material persists, the focus remains infective, and the organisms, though quiescent, are alive.

3. **Calcification** may follow caseation if the cheesy products become encapsuled and almost all the fluid is absorbed; the deposit of lime-salts in this cheese-like material converts it either into a gritty mass or into an irregular stony body. Caseous mesenteric glands are especially prone to this change. Calcification principally affects very old limited lesions. When the calcification is complete, the lesion ceases to be infective.

Sections of the small calcareous particles, when decalcified and examined under the microscope, are seen to consist of a series of concentric layers. These layers are composed of a substance which, according to Metschnikoff, gives the same reactions as that forming the envelopes of the tubercle-bacilli. Arguing from his experiments on Algerian rats, he maintains that these layers are formed by degenerative changes in the bacilli within the giant-cells, and that they subsequently become infiltrated with phosphate of calcium. They are, therefore, to be regarded as by-products of the struggle between the cell and the bacilli.

4. Softening. (*Chronic Abscess.*)—Caseous masses do not always dry up and become encapsuled, but often soften and break down into the pus of a chronic abscess; and even when they have become encapsuled and calcified, softening may occur round about them: a chronic abscess forms, and the dead material is discharged. While the smaller encapsuled foci, and especially those which lie deep in the substance of organs, become dry and calcified, the extensive, diffuse lesions, and those lying near a skin or a mucous surface, tend to soften: in other words, the less the resistance of the tissues, the greater is the tendency to softening. It seems that some irritation of the tissues is the cause of the exudation of fluid into the caseous mass, and that this exudation changes the latter into a chronic abscess; for an examination of the "pus" of a chronic abscess shows that it consists chiefly of fatty granules suspended in fluid, with here and there a fattily degenerated granular leucocyte. It is thus quite different microscopically from that of an acute abscess (p. 172). It differs also to the naked eye, being generally whiter and thinner than true pus, while it often contains curdy masses, which may be either gritty or stony from calcification. The large majority of chronic abscesses are of tubercular origin. So chronic is the process that there is often no sign of inflammation until just before the "abscess" bursts, when the tense skin, where it is pointing, becomes red, shiny, and progressively thinner. Ultimately the epidermis bursts, and the cavity discharges its contents. The wall of such a cavity is lined by a thick layer of pale purplish granulation-tissue, in which are yellow foci. This lining is so loosely adherent to the surrounding tissues that scraping with a sharp spoon easily detaches it, and brings it away either entire or in large pieces. The tissues beyond it are not infiltrated. It is very important that this lining should be removed from such abscesses, as well as the base of any ulcers resulting from their rupture; for it is in these portions that the tubercle-bacilli reside, and healing is impossible until the diseased layer with the infecting organisms has been removed and replaced by healthy granulation-tissue. The contents of these abscesses are infective, and produce general tuberculosis when injected into animals.

This account of the formation of a chronic abscess holds good in all cases—in the subcutaneous tissue (*subcutaneous strumous nodule*, so common in children); in a lymphatic gland (*strumous abscess*); in the lung, where sooner or later it bursts into a bronchus, discharges its contents,

and forms a *cavity* or *vomica;* in the thickened synovial membrane of a tuberculous joint (*white swelling*); and in bones, as is seen in *caries of the spine.* The chronic abscesses which arise in connection with deep bones, especially those of the spine, are frequently called *gravitation abscesses*, because the "pus" often extends long distances among the soft parts, usually in the direction toward the feet, before it reaches the surface. But extension by no means always occurs in this direction, and, when it does occur, is not arrested by placing the patient in the horizontal position. We may therefore conclude that in these, as in all other cases, the "pus" spreads in the direction of least resistance, and that gravity has comparatively little to do with it. Instances have been recorded of such an abscess starting from the lower dorsal or lumbar vertebræ, entering the sheath of the psoas, causing gradual absorption of its muscular fibres, working its way beneath Poupart's ligament, taking the course of the profunda artery, passing through the adductor magnus into the popliteal space, penetrating between the superficial and deep posterior leg-muscles, and finally pointing by the inner malleolus. Such an abscess is contained in a dense fibrous sheath, formed by inflammatory thickening of the natural connective tissue. The sheath is sometimes strong enough to be dissected out entire. The cavity is crossed by fibrous bands, which may contain vessels, and care must be taken lest a finger introduced during life tear them. The inner lining of the wall of the cavity is but slightly vascular—the contrast between the chronic and acute abscess in this respect being very marked. It is usually coated with a cheesy deposit of irregular thickness, outside which lies a very thin layer of granulation-tissue. At the upper extremity is the diseased bone—the *fons et origo malorum.*

Infection of Other Parts.—1. **By Lymphatics.**—In this way masses of *conglomerate tubercle* (p. 336) and patches of infiltrating tubercle, such as those of the skin (*scrofuloderma*), are formed. It is supposed that leucocytes enter the primary focus, take up bacilli, and wander out again along fine lymphatics into the surrounding tissues, there to sicken and die not far from the parent mass. A fresh tubercle thus forms and caseates, and its margin coalesces with that of the parent mass, which in this way gradually enlarges. The young tubercles form the grayish translucent ring, with here and there an offshoot, seen round the conglomerate mass. Leucocytes containing bacilli, and free organisms are also carried by the lymph-stream to the nearest gland. Thus, the process of infection of mesenteric glands from an intestinal ulcer may sometimes be traced by the presence of tubercles along the track of the lymphatics. Infection by lympatics is most frequent when there is a marked lesion at the point of entry—*e. g.*, in tubercular ulceration of the intestine. Tubercles have been found in the thoracic duct in cases of acute tuberculosis; this is evidence that the bacilli passed by this channel to the blood.

The *lymphoid tissue* is not only the medium by which the disease spreads, it is also the place where the tubercle-bacilli are most actively

attacked, and where therefore they are most likely to be destroyed. If the organisms pass the lymphoid follicles in the mucous membrane, they have still to deal with the lymphatic glands beyond.

A somewhat strained analogy has been drawn between the collections of lymphoid tissue distributed along the mucous surfaces and the fortified towns which guard a frontier. The lymphoid masses serve as garrisons from which leucocytes issue out and deal with any organisms they may chance to meet. Unfortunately the discriminating power of the phagocytes is not equal to the occasion, and they sometimes carry back within them bacilli whose subsequent development reminds one of the old story of the Trojan horse.

2. By some Natural Passage.—A sudden inspiration following the bursting of a tuberculous focus into a bronchus draws the infective material into many of the smaller bronchi, with the result that a caseous broncho-pneumonia develops simultaneously in many parts of the lung. In the same way the palate may be infected from the tongue, the intestine from swallowed sputum, and the lower urinary tract from the kidney.

3. By Bloodvessels.—The walls of bloodvessels, especially in the lung, may be affected by tuberculosis. The caseating foci may rupture into the lumen and the bacilli be carried in the blood-stream to distant parts. The thoracic duct may also act as the channel by which the bacilli reach the blood-stream.

In one or more of these different ways the organisms reach the blood and are carried all over the body, developing when and where the conditions are suitable—in the lungs, meninges, joints, or other parts. If the supply of bacilli is plentiful, the case is likely to be acute.

General Infection.—An acute miliary tuberculosis of the meninges, lungs, peritoneum, and various abdominal viscera plainly implies that a large number of bacilli have found their way within a short space of time into the blood: the result is similar to that following the intravenous injection, in rodents, of a syringeful of a pure cultivation of the bacilli. To provide the large number of organisms necessary to produce this general infection, multiplication must have first occurred in some part of the body. The focus, in which this multiplication most often takes place, and whence general infection usually starts, is a caseous bronchial gland. The caseous matter probably enters directly into the blood-stream, by means of an opening formed by ulceration into a small vein or artery. Acute miliary tuberculosis may, however, spread from any localized focus containing living bacilli. Extension by means of a lymphatic vessel leads to the formation of tubercles along this vessel, or in glands through which the lymph passes. If the thoracic, or right lymphatic, duct be affected, the organisms find their way into the systemic veins. They next reach the lungs, and the bacilli are so small that they may easily pass through the pulmonary capillaries into those of the systemic circulation.

Limitations of General Infection.—The term *acute general miliary tuberculosis* has hitherto been used in contradistinction to *localized tuber-*

culosis—*e. g.*, a mass of conglomerate tubercle in the brain, or a caseous gland. But even a "general" tuberculosis, due apparently to the rapid entrance of numbers of organisms into the blood, is far from being really general; for while the lungs, spleen, liver, kidneys, testes, and meninges are very frequently affected, the voluntary muscles, mammæ, ovaries, and thyroid gland nearly always escape. Thus a series of regular gradations occur, commencing with (1) the most wide-spread miliary tuberculosis, and including successively (2) cases of miliary tuberculosis limited to the meninges or peritoneum; (3) cases of multiple infiltrating tuberculosis—*i. e.*, tubercle limited to glands, skin, or bones and joints; and finally (4) cases in which a single spot of skin, a single joint, or a single gland is affected.

The selection of special organs in "general" tuberculosis seems to indicate **local predisposition** on the part of these organs. In this way the limitation of the infection to the meninges can be explained. There is no reason for assuming that the bacilli are arrested in them rather than in other parts. The same explanation appears applicable to cases of limited miliary tuberculosis, and may possibly be the reason why tubercular meningitis affects the base rather than the convexity of the brain. Again, there seems no other explanation to offer of what seems to be a well-established clinical fact—viz., that children who suffer from multiple lesions of skin, glands, bones, and joints do not develop visceral tuberculosis nearly so often as those in whom a single joint is affected.

Next, with regard to the *dose of organisms:* this may be large or small. It may be single, or it may be repeated at longer or shorter intervals. The different doses may come from the same or from different foci, giving rise to successive "crops" of tubercles, distinguishable after death—the more recent being small and gray, and the older large and yellow. When only a few bacilli enter the circulation at one time, the infiltrations which they excite reach a far larger size than they could possibly attain in the speedily fatal cases of general tuberculosis. Many of the cases in which single glands are affected are doubtless due to infection from small wounds or tubercular sores, either of the skin or of the mucous membrane from which they obtain their lymph-supply. But many cases of localized tuberculosis, especially of bones and joints, admit of no such explanation: these Koch believed to be due to the entry of a single bacillus into the circulation and its lodgement in the affected part, and considered that in these cases—as in those of wide-spread infection—the organism is obtained from some primary focus, usually a bronchial gland, whence it has, as it were, accidentally slipped by the lymph-path into the blood. He thought it highly improbable that even a single organism could pass from an alveolus into a capillary of the lung without causing a tubercular focus on the way.

The *seat of infection* may assist in explaining some peculiarities of the disease, and should be borne in mind.

It is impossible to explain why some tubercular processes remain

local, whilst others generalize. Blocking of lymphatics, exemption of the walls of blood-vessels, feeble local growth of the bacillus, healthy resistance on the part of the tissues in general, may afford hypothetical explanations.

Etiology.—The circumstances leading to infection by the tubercle-bacillus far outweigh all other considerations, and these have already been described.

Age and Sex.—The disease is very prevalent during the first two years of life. The death-rate then falls, and remains low until about the tenth year, when it begins to rise again. The rise begins some years earlier in the case of girls than in that of boys, though, when all ages are considered together, the sexes are found to be equally affected. Tubercular disease is often apparently quiescent during pregnancy, but is frequently fatal soon after parturition; and death from phthisis is often attributed to "childbirth."

Heredity.—There is a firm belief in the hereditary nature of tuberculosis, and especially of pulmonary tuberculosis. From the statistical point of view the belief probably rests on stronger evidence than has yet been adduced, for many cases of tuberculosis die unrecognized, and in many others the disease is arrested—neither of these classes appearing in the statistics.

Three explanations of the influence of heredity in tuberculosis have been put forward:

(1) It is suggested that all cases are due to infection from the outside alone, and that heredity acts either (*a*) by subjecting the individual to more than the average chances of infection, and causing him to live in infected rooms with infected persons, and to use infected articles; or (*b*) by aiding in the development of habits (for example, alcoholism) which render him less resistant to invasion. There can be but little doubt that this explanation is, in a large number of cases, correct, but it certainly is not universally applicable; for, in many instances, long intervals elapse between the death of a parent from phthisis and the outbreak of the disease in the children; while the locality, house, and general surroundings are all different. Furthermore, it has frequently been noted that, even when the children of a phthisical parent are widely separated and living average healthy lives under diverse conditions, they still seem especially liable to infection.

(2) According to Baumgarten, the solution of this question lies in the actual transmission of the bacillus from parent to embryo, and in its latent existence in the tissues for many years. According to him, infection may occur before or about the time of fertilization; the bacilli reaching the uterus from the peritoneum through the Fallopian tube, or gaining access with the spermatozoa. The evidence in support of this view is derived almost exclusively from experiments on animals. It seems to be reasonably certain that tubercle-bacilli and some other organisms can exist for, at any rate, some weeks in a quiescent state among actively growing cells, and later on multiply and produce their

usual effects. One of the experiments showing this may be quoted. Fertilized hens' eggs were inoculated with tubercle-bacilli; the chicks were hatched at the ordinary time, and were normal in appearance. Three weeks later tuberculosis rapidly developed. There is certainly some reason to believe that tubercle-bacilli may exist for a time in tissues without producing tubercles. They have been found in the apparently healthy testes and prostate in cases of tuberculosis of other organs; while the fœtus of a phthisical mother has served to infect animals though itself apparently free from disease. But if these organisms often exist in seminal discharge and thus affect the ovum, it is at least curious that tuberculosis of the female generative organs is so rare; nor is it easy to believe that bacilli can lie latent in the body for ten or twenty years. Furthermore, this theory in no way explains the peculiarities of the disease as regards age or sex, which have been already alluded to. The possibility of this form of hereditary influence must be decided by further investigations.

(3) The least definite, but the most probable, explanation is that of some special predisposition of the tissues to tuberculosis (p. 356), such as is now generally recognized to exist, in a less degree, in the case of such diseases as typhoid fever and diphtheria. In no other way can the objections to the other explanations be met. We have no knowledge of the physical factors in which this predisposition consists. A small flat chest and a tendency to catarrh are often present in people who ultimately develop phthisis; and the absence of free respiratory movements is held to favor the development of the bacilli. The recovery of certain cases of phthisis is explained on the assumption that the soil which was at one time favorable to the growth of the bacillus became at a subsequent period unfavorable; and as tuberculosis is readily arrested in some individuals, it is not unreasonable to suppose that in others the bacilli are not even able to multiply and give rise to their characteristic lesions. It is quite certain that some animals are far more susceptible than others to the disease.

Immunity to tuberculosis may be produced in animals by inoculation with attenuated bacilli, or with bacilli belonging to a different strain. Koch has endeavored to raise the resistance of persons already infected with tuberculosis, by injecting them with a solution of the bodies of the bacilli (*new tuberculin*) or with the actual bacilli suspended in an emulsion. The value of these methods of procedure is still undecided. The serum of healthy persons possesses some power of neutralizing the toxines of the tubercle bacillus; that of tuberculous patients is said not to have this power (Mircoli). Destruction of the bacilli is probably effected by leucocytes, aided by some special substance developed in the serum.

Tuberculosis of the Larynx.

Tuberculosis of the larynx (*Laryngeal Phthisis*) is generally secondary to tuberculosis of the lungs, and is then due to infection from the sputum. It commences as sub-epithelial tubercles, situated

chiefly in the aryteno-epiglottic folds, on the cords, and on the under surface of the epiglottis. These may be few or numerous, and may ulcerate early—especially on the cords—or may multiply and form a diffuse infiltration, which in the aryteno-epiglottic fold produces a pear-shaped swelling with its large end toward its fellow in the mid-line. The caseous masses rupture and ulcerate. In this way considerable masses of tuberculous graulation-tissue may be formed above the vocal cords. Later on, secondary infection with pyogenic cocci may lead to abscesses and necrosis of cartilage, to hectic fever, exhaustion and death. Tubercular ulcers may sometimes be distinguished from those due to syphilis, or to new-growths, by the small amount of new tissue in their floor and margins, and by the absence of cicatrices.

Tubercular ulcers in the trachea are usually small and superficial, and also arise from the breaking down of sub-epithelial tubercles. Occasionally they are both deep and extensive, and may be followed by abscesses and necrosis of the cartilages.

Tuberculosis of the Lungs.

In pulmonary tuberculosis are found the most varied manifestations of the growth and action of tubercle-bacilli.

The infecting organisms may be brought to the lungs (1) by the blood, (2) by the lymphatics, and (3) by the air-passages.

1. **Infection by the Blood.** (*Hæmatogenous Pulmonary Tuberculosis.*)—Although in a few cases no primary focus can be found, this form of infection must be regarded as secondary to tuberculosis of some other part. The bacilli enter the circulation from the rupture of a caseous nodule in some distant artery or vein, or from the lymphatic system by way of the thoracic duct, and are arrested in the alveolar capillaries.

When large numbers of bacilli are thus uniformly distributed throughout the lungs, innumerable giant-cell systems make their appearance in the alveolar walls (Fig. 197). The capillaries in their immediate neighborhood are destroyed, and the adjoining alveoli become filled up with desquamated epithelium and leucocytes (Fig. 198). By this time the tubercle is spheroidal in shape, and visible to the naked eye—gray tubercles being generally composed of two, three, four or more giant-cell systems. Enough caseation to give the tuberculous nodules a slightly yellowish appearance may, in some instances, follow. A little later, the development of fresh giant-cell systems on the borders of these yellow tubercles and the inflammatory exudation into the alveoli and alveolar walls make them larger and less sharply defined; but in these cases many other organs may be affected simultaneously, and death supervene before any marked destruction of tissue takes place. The smaller bronchial tubes may be hyperæmic and contain an excess of mucus, and minute patches of emphysema and collapse may be found. When the infection is more limited and the tuberculous foci are fewer, life is more prolonged and the usual secondary changes have

time to occur. Occasionally the infection may be limited to one more terminal arteries. The changes will then be lobular in distrib

FIG. 197.

Acute tuberculosis of lung. a, a^1, a^2, a^3, recent tubercles, each made up of several giant systems, in which the giant-cells are more deeply stained. In the centre of a^3 mar caseation has occurred; b, b^1, small bronchial tubes, at one point ulcerated and dilated. engorged vessels (b); c, contents of bronchial tube: these consist principally of mated epithelium and leucocytes; d, small branch of pulmonary artery. × 20.

tion, and the case approximate in its development to one of infec through the air-passages, presently to be described.

FIG. 198.

A portion of a small soft gray tubercle in the lung. From a case of acute general tuberculosis. An alveolus is filled with epithelial elements and a few small cells; there is also some lar infiltration of the alveolar wall. × 200.

Pathology.—The differences in the histological characters and devel- opment of the lesions in acute miliary tuberculosis of the lung depend

to some extent upon differences in the age of the nodules, but are mainly due to the number and rapidity of growth of the organisms in each focus. If the bacilli be numerous and multiply rapidly, the tubercles will consist in the main of accumulations of epithelium within the pulmonary alveoli, and will rapidly undergo caseation (Fig. 199). If the growth of the bacilli be less active, typical "giant-cell systems" will form and the nodules will attain a more advanced age; while degeneration will be less rapid and complete (Fig. 197). Lastly, if the organisms be very few and their multiplication slow, as in the least intense and most chronic processes, the proliferation of the tissue-cells reaches its maximum (Fig. 198), and considerable fibroid induration results. Degeneration takes place slowly, and is limited to the central portions of the nodule. A close analogy can thus be drawn between the tissue-changes resulting from tuberculosis of the lungs and those which result from other chronic inflammatory processes (p. 173).

2. Infection by the Lymphatics. (*Lymphogenous pulmonary tuberculosis.*)—Not infrequently, especially in children, tubercle-bacilli may reach the bronchial glands by means of the air-passages and bronchial

FIG. 199.

A gray tubercle from the lung in a case of acute general tuberculosis. The whole of the tubercle, which was surrounded by normal lung, is shown. It consists principally of intra-alveolar products. × 35.

lymphatics without producing any local lesion in their track. On rare occasions the bronchial glands may also be infected through the diaphragm from the mesenteric glands. In both cases the substance of the lung may be infected from the resulting tuberculous glands. Infection generally proceeds in a somewhat radiating manner from the root of the lung by means of the lymphatics, and especially by those that lie under the pleura.

It occasionally happens that a local tubercular disease of the lung

and pleura may follow that of an adjoining rib or vertebra. From such a centre the disease may spread in any of the usual ways.

The nature and progress of the lesions in no way differ from other forms of tuberculosis in which the lymphatics are involved.

3. Infection by the Air-passages. (*Pneumatogenous pulmonary tuberculosis.*)—This form of pulmonary tuberculosis, commonly known as "phthisis," is almost invariably the result of inhaling tubercle-bacilli with the respired air (p. 346). In exceptional cases it may be due to the discharge of the contents of a caseous nodule in the larynx, or to the rupture of a caseous bronchial gland into a bronchus. Whichever be the method of infection, the bacilli find their way into the alveoli, and the disease follows the same course; though in cases of ruptured bronchial glands, the foci of infection are more numerous, and spread more rapidly, because enormous numbers of bacilli are thereby simultaneously introduced, whereas in the case of ordinary infection probably not more than two or three are deposited at a time.

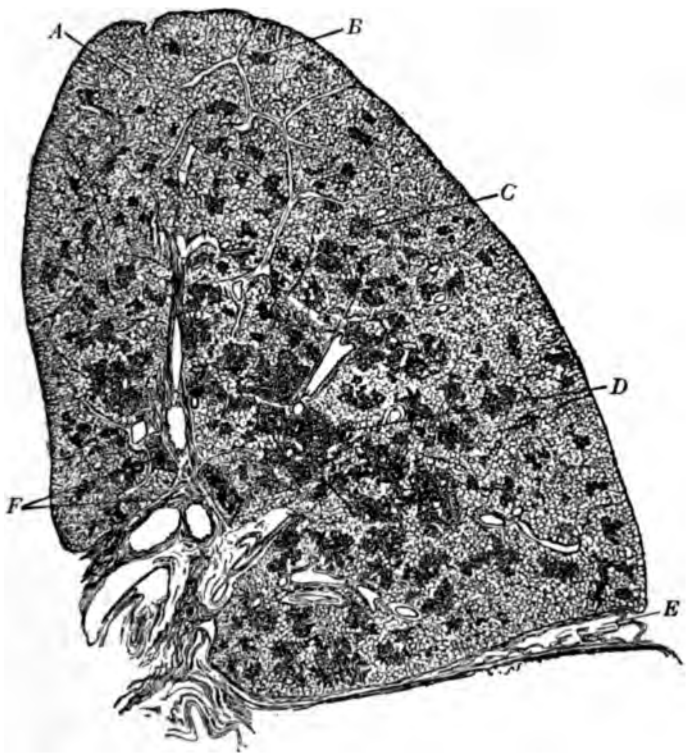
In adults, the first sign of infection is generally the presence of tubercular changes in the upper lobe of one of the lungs—more often of the left—near the apex. The few tubercle-bacilli which are deposited in the bronchioles, alveoli or lymphatics, and which escape destruction, multiply and give rise to a number of giant-cell systems, consisting of proliferated epithelium and connective tissues with varied proportions of leucocytes in the periphery. Ordinary gray tubercles are thus formed in the way already described (p. 350). These gradually develop into larger nodules with caseous centres (yellow tubercles), or rapidly give rise to patches of broncho-pneumonia. If the walls of neighboring arterioles become involved and weakened by the formation of tubercles, the vessels may rupture, and minute hemorrhages occur, giving rise to the slight hæmoptysis which is so frequently met with in early phthisis.

While these changes have been taking place, a considerable amount of fibrous tissue may have developed—an amount sufficient, in some instances, to enclose the whole of the diseased area, which gradually shrinks until it forms a small cheesy nodule with a thick fibrous envelope, or a deeply puckered scar at the extreme apex of the lung without any remaining sign of the original caseation. These are the most favorable terminations of the infection. Not infrequently, however, while the development of fibrous tissue is marked at one part where the disease is quiescent it is almost absent at others where progressive infection is occurring through the medium of the lymphatics. It is generally observed that, long before the whole of the upper lobe is involved, tubercles make their appearance at the apex of the lower lobe. It is sometimes held that this fresh infection is due to the implication of the bronchial glands from the original foci, and to the subsequent transmission of the bacilli mainly by the subpleural lymphatics; but it is most likely the result of direct infection by the air-passages—the inhaled bacilli being derived either from the sputum or from an external source similar to that which gave rise to the primary disease. Secondary infec-

tion will be promoted by forced inspiration, the result of active exercise (Fig. 200).

The subsequent changes are so varied that it is impossible in a short description to include all the possible appearances to which the disease may give rise. The spread of the original foci involves large tracts of tissue, and the intervening parts of the lung, which are at first unaltered, become invaded either by tubercular nodules or by ill-defined,

FIG. 200.

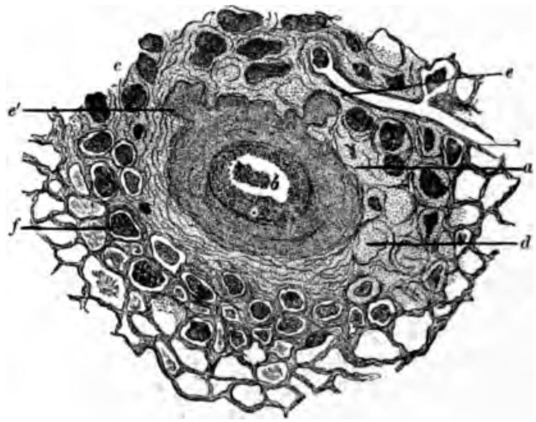


Pulmonary tuberculosis. Section through upper lobe of right lung, seen from behind. Secondary infection from lung of opposite side by means of air-passages. The tubercular masses are mainly grouped round the smaller bronchial tubes, while the lymphatic glands are only slightly involved. *A*, normal lung; *B*, small tubercular nodule; *C*, larger tubercular nodule; *D*, large mass of tubercle; *E*, adherent interlobar pleura; *F*, bronchial glands with pigment. × ⅔.

scattered broncho-pneumonic patches which spread and in many places become confluent. If various consolidated portions of a phthisical lung be examined microscopically it will be found that, excluding those parts which obviously consist of large areas of caseating or fibroid tissue, the following changes can in most cases be made out: (1) An accumulation of epithelial or other cells within many of the alveoli; (2) a cellular infiltration and consequent thickening of the alveolar walls, together

with a similar change in the walls of the terminal bronchioles; and (3) an increase in the interlobular connective tissue. These changes are generally associated, although some of them are more prominent

FIG. 201.

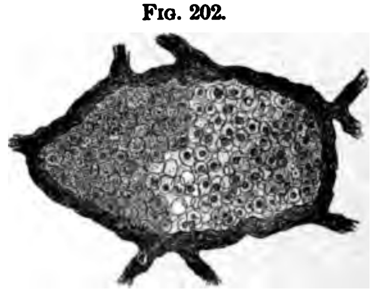


Acute phthisis. A transverse section of a terminal bronchus with the surrounding alveoli, showing the *lobulated* character of the pulmonary consolidation. *a*, Thickened and inflamed bronchial wall; *b*, cavity of bronchus containing a little mucus; *c*, alveoli filled with catarrhal products; *d*, remnants of obliterated alveoli and alveolar contents, which have undergone caseation; *e*, *e'*, inflammation spreading to alveoli; *f*, thickened alveolar walls. × 25.

and characteristic than others. The special prominence of any one of them helps to produce those variations in the physical characters of the lungs which are met with in the different stages and in the different varieties of the disease.

1. *An Accumulation of Cells within the Alveoli.*—This is one of the most frequent changes met with in phthisis, and is precisely similar to

FIG. 202.

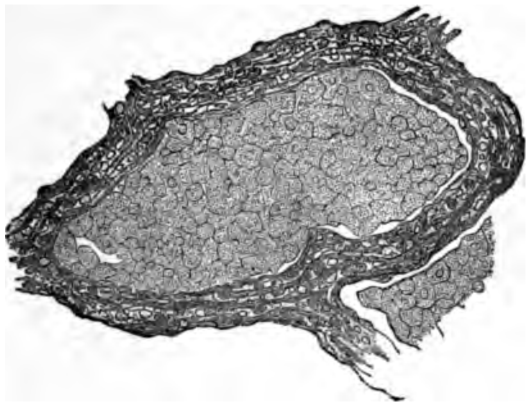


An alveolus from a small soft gray tubercle in the lung. From a case of acute tuberculosis. The alveolus is filled with epithelial elements and a few small cells; there is also some cellular infiltration of the alveolar wall. × 200.

that which will be described as occurring in other varieties of broncho-pneumonia. The alveoli are generally found filled with the offspring of the epithelial cells which normally line the alveolar walls (Fig. 202). In some acute cases of phthisis, this alveolar accumulation may at first

constitute almost the only morbid change, and although there is always some cell-infiltration of the alveolar walls, the great bulk of the pul-

FIG. 203.



Acute phthisis. Showing one of the alveoli filled with degenerating epithelial elements, and marked cell-infiltration of the alveolar wall. × 200.

monary consolidation is due to the distension of the alveolar cavities with catarrhal products (Fig. 204). In some parts—those in which

FIG. 204.

Section of lung from a case of acute phthisis, in which the consolidation consists almost exclusively of products accumulated within the alveoli. In some parts a free space is seen between the alveolar walls and their contents; this is due simply to the shrinking of the latter caused by the hardening of the specimen. × 50.

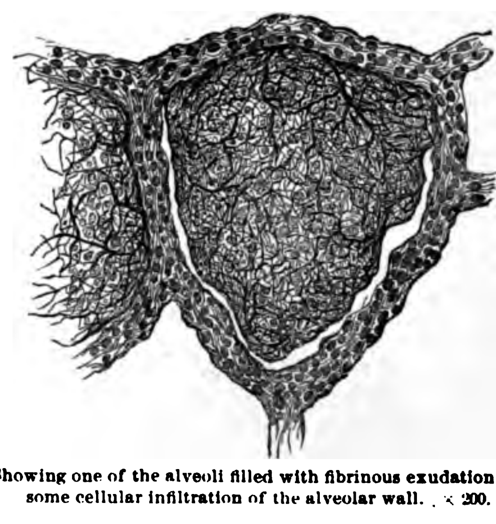
the change is the most recent—the alveolar walls and the large cells which fill the alveoli are but little altered, but in the greater portion of the consolidated tissue the cells are seen in various stages of degeneration (Fig. 203) and the alveolar walls are destroyed; whilst in those tracts of tissue in which the process is most advanced all

trace of structure is lost, and nothing remains but the granular débris seen in caseated tissues. These changes are precisely similar to those met with in the larger nodular lesions of acute general tuberculosis (Fig. 192).

Less frequently the contents of the alveoli are similar to those met with in ordinary croupous pneumonia (Fig. 205), but they are usually associated with more or less epithelial proliferation.

The *naked-eye appearances* presented by the lungs, in those cases in which the pulmonary consolidation is chiefly due to *intra*-alveolar changes, are very characteristic, partly on account of their distribution, but mainly because of the rapid degeneration and caseation which they, together with the alveolar walls, undergo. The consolidation, although sometimes almost uniform, generally presents a somewhat lobulated outline, indicating the implication of different groups of the pulmonary lobules. The consolidated tissue is soft and friable, breaking down very readily under the finger, and there is complete absence of any induration. The color varies from a reddish- to a yellowish-gray, while small portions of a more decidedly yellow tint are often scattered

FIG. 205.



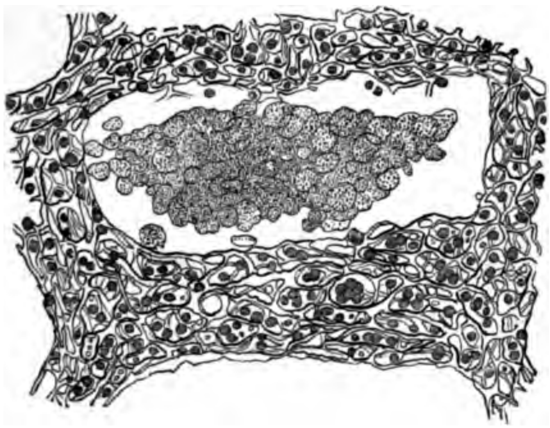
Acute phthisis. Showing one of the alveoli filled with fibrinous exudation and leucocytes, and some cellular infiltration of the alveolar wall. × 200.

through the consolidated mass. These scattered areas correspond with the parts in which the retrogressive changes are the most advanced, and they are even softer in consistence than the surrounding tissue. In many parts the consolidated and caseated tissue will be found broken down, so as to form sinuous cavities of various sizes. These possess irregular walls, which are soft and friable, like the consolidated lung surrounding them.

2. *A Cellular Infiltration and Thickening of the Alveolar Walls, and, in most Cases, of the Walls of the Terminal Bronchioles.*—This is a frequent change, especially when the progress of the disease is somewhat

slow and the consistence of the consolidated tissue firm. In its earlier stages a few small cells are seen infiltrating the alveolar septa, which are thus slightly thickened (Figs. 203 and 205). As the change proceeds the number of these cells increases, and from them an imperfect fibro-cellular structure is developed (Fig. 206). As the new tissue

FIG. 206.



Section of lung from a case of somewhat chronic phthisis. Showing the thickening of the alveolar walls by the formation of epithelioid cells, and an accumulation of epithelial cells within the alveolar cavity. The latter are undergoing fatty changes. × 200.

develops in the alveolar walls it gradually obliterates and replaces the alveolar cavities, so that, whilst in some portions the thick-walled alveoli may be found still containing epithelial elements, exudation-products, or even giant-cells, in others large tracts will be seen, consisting almost entirely of the small-celled growth. The development of this new tissue in the alveolar walls is attended by obliteration of the pulmonary capillaries, thus assisting the action of the bacilli in the production of the subsequent caseation (p. 344).

The changes which may subsequently take place in this alveolar growth vary. The infiltrated septa may rapidly caseate before any marked thickening or development of new tissue has had time to occur, whilst in other less acute cases there is a considerable development of the imperfect fibrous tissue. Yet, although this may remain as a more or less permanent structure, it usually undergoes in its turn similar caseation. These two kinds of change are often found simultaneously in the alveolar walls of different parts of the same lung. In those portions in which the new tissue is undergoing *degeneration* it becomes converted into a structureless granular débris, any cells which may be contained within the alveoli meeting with a similar fate; whilst, in the immediate vicinity of these degenerated portions, a more permanent fibrous *structure* may be found.

Respecting the *naked-eye changes* which the growth of this small-celled tissue produces in the lungs, it may be stated generally that it

usually leads to some induration of the pulmonary tissue. The e
of this induration will vary according to the characters of the new t
If the tissue remain almost entirely cellular—as is the case wher
very rapidly formed, and when new vessels do not develop—it
produce little or no induration of the consolidated area; and this
solidation, consisting mainly of degenerating cells both in the wall
cavities of the alveoli, will be soft and friable in consistence,
resembling that already described. When, on the other hand,
more frequently the case, there is any considerable developmen
fibrous tissue; when the reticulum is dense and abundant; and
vessels develop and persist, there will be a corresponding indurati
the consolidated tissue. In many cases these changes produce un
tracts of indurated consolidation of a grayish color mottled with
pigment. Scattered here and there among them may be seen yell
patches corresponding to the portions which have undergone retro
sive fatty changes.

Fig. 207.

Chronic phthisis. Showing the new interlobular fibrous growth surrounding and encaps
a degenerated and caseous portion of the consolidated lung. × 25.

3. *An Increase in the Interlobular Connective Tissue.*—This is
with, to a greater or less extent, in all the more *chronic* form
phthisis. This tissue, which surrounds the bronchi and bloodve
and contributes to the formation of the alveoli, is found not on
creased in amount, but also altered in character. Its structure i
that met with as the result of proliferative inflammation in other o
(Fig. 207). It has a much greater tendency to develop into a p
nent fibrous tissue than has the interalveolar growth, and it is

the seat of those retrograde changes which are so frequent in the tissue originating in the alveolar walls. Intermingled with this new fibrous tissue are granules of black pigment. These differences in the structure and termination of the interalveolar and interlobular growths are accompanied by corresponding differences in their vascular supply. Whereas in the *interalveolar* growth the pulmonary capillaries become obliterated and new vessels are rarely formed, or, if formed, are often subsequently destroyed; in the *interlobular* growth the new vessels formed generally persist. In the most chronic cases of phthisis this interlobular fibrous growth may constitute the predominant structural change, and large portions of the lung may be found completely replaced by it.

An increase in the interlobular connective tissue in phthisis—inasmuch as the new tissue tends to become dense and fibrous—leads to extensive induration of the pulmonary tissue; and further, owing to the contraction which the new tissue undergoes, its growth ultimately produces a corresponding contraction of the diseased lung. In all those cases of phthisis in which there is either a marked thickening of the alveolar walls or an increase in the interlobular connective tissue, any cavities which may exist in the consolidated and indurated tissue are characterized by the tough fibroid structure and the smoothness of their walls. These present a marked contrast to the soft friable tissue surrounding the cavities in cases where the pulmonary consolidation is due mainly to intra-alveolar changes.

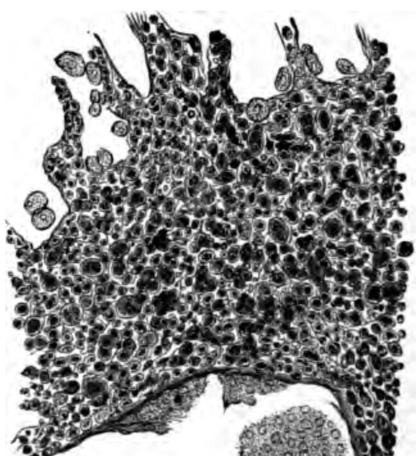
Changes in the Bronchi.—Sometimes the walls of the bronchi are directly invaded by the bacilli. In other cases only bronchial catarrh is present. The catarrh is sometimes general, but much more commonly it is limited, and more strictly confined to such portions of the lung as are becoming, or have already become, consolidated. In many cases there is a marked tendency of this bronchial catarrh to lead to extensive cell-infiltration of the deeper structures of the bronchial wall (Fig. 208). This cell-infiltration sometimes leads to the production of small *ulcers*. These have thickened opaque edges, and when once formed they tend to increase. In addition to these changes in the bronchial mucous membrane there is often a cellular infiltration of the peribronchial tissue, and here tubercles are often met with, especially round the smallest bronchi. In very chronic phthisis, bronchiectasis may occur (see Chap. XI.).

Changes in the Arteries.—Bands of fibrous tissue frequently extend from side to side across a large cavity. These were formerly supposed to contain large arteries, but in all probability this is seldom the case. When an artery traverses a newly formed cavity it may happen that inflammation of the walls leads to thrombosis and subsequent obliteration of the lumen, before the advancing disease can destroy its walls and give rise to hemorrhage. Occasionally, in the case of a small cavity, an artery may be weakened at one spot by the partial softening and yielding of its walls owing to tubercles formed in them, and an aneurism result before any thrombosis has occurred. Such an aneurism

may fill the cavity and for a time increase *pari passu* with it. Before the aneurism has attained a diameter of an inch it will in all probability rupture: severe hemorrhage may thus result, and may be fatal, either from asphyxia, due to inhalation of a large quantity of blood into the air-passages, or more often from syncope, due to the great loss of blood. Tubercular arteritis may also lead to general infection and to death from general tuberculosis.

Summary.—To sum up, in the most acute forms of *phthisis* the principal lesion is an infective tubercular broncho-pneumonia, in which the affected parts tend to undergo caseation, and in which giant-cell systems play but a small part. The centres of the caseated portions liquefy and may be discharged as sputum by the air-passages; thus small sinuous cavities are formed. When the change is more local and less acute, the caseated areas and the resulting cavities are often larger in size, but more limited in distribution. If the progress is still more gradual, fibrosis—an indication of repair—gives rise to induration in the consolidated tis-

FIG. 208.



Tubercular inflammation of a bronchus. Section of a small bronchus of a child, who died from miliary tuberculosis. The deeper structures of the bronchial wall are seen to be extensively infiltrated with cells, mainly of the epithelioid type. The infiltration extends to and invades the walls of the adjacent alveoli, which are seen at the upper part of the drawing. The cavity of the bronchus contains a little mucus, *m*. × 100.

sue, limits the spread of the cavity, and by its further development and contraction may lead to a practical healing of the diseased tissue. It must, however, be remembered that, unless all the tuberculous foci undergo complete fibrosis, there is always the possibility of secondary infection, for the presence of the caseated material is evidence of the continued existence of the bacilli. Two varieties of cavity have already been described, and these may be taken as types—the one rapidly

formed, with ragged irregular walls of softened and breaking-down lung tissue; the other, possessing dense, smooth, fibrous walls, lined perhaps by a layer of granulation tissue, which continues to secrete a purulent fluid. Many intermediate varieties will, however, be met with even in the same lung. Thus an old cavity may open into a bronchus and give rise to extensive infection of a neighboring part, in which soft-walled cavities may be rapidly formed. In some of the consolidated tissue surrounding these, fibrosis may gradually occur, and thus may be produced cavities with walls showing every form of gradation between the two types previously mentioned.

Etiology.—Most of the questions concerning the cause of tuberculosis of the lung have been considered in the section on General Tuberculosis (p. 357). It only remains to inquire why the apex of the lung is so frequently the earliest seat of the disease, especially in those cases in which the infection arises from inhalation. The causes are probably to be sought for in the diminished range of respiratory movement which obtains in the highest portions of the lungs. As a result of this diminished movement there is diminished aëration of blood, and, in certain conditions of health, a tendency to stagnation of the blood-stream in the capillaries. The stagnation of the circulation may lead to more or less injury of the walls of the vessels, and the growth of any tubercle-bacilli that may have gained entrance may be thereby favored. There may also be diminished power of expelling irritant particles (bacteria, etc.) which effect a lodgment in this region.

It is obvious that any inherited or acquired weakness must assist in the occurrence of these apical changes. General feebleness and want of vigor lead to loss of muscular strength and weakness of the heart, and thus tend to prevent the full expansion of the chest, and to cause a stooping posture of the body—conditions favoring blood stagnation in the highest portions of the lungs. Further, the success, as a means of treatment, attributed to residence in a rarefied atmosphere is probably dependent on the increased rhythmical expansion of the lungs.

Tuberculosis of the Kidney.

In acute generalized tuberculosis miliary tubercles may often be found in the cortex of the kidney, and more rarely in the medulla. In other cases masses of caseating tubercle occur in one or both kidneys. The disease may extend and produce almost entire destruction of the organ affected, the kidney being converted into little more than a shell containing breaking-down caseous material. Secondary suppuration may occur in the tubercular cavities formed, and pus is generally present in the urine, in which tubercle-bacilli may be demonstrated by appropriate methods. The disease usually involves both kidneys before death, though it may be much more advanced on one side than on the other.

Tuberculosis of the Pia Mater and Brain.

In the pia mater the tubercular process is associated with inflammation of the meninges and superficial parts of the brain, and is known as **tubercular meningitis**, or, more accurately, *meningo-encephalitis*. This is almost invariably the result of infection from a distant focus, though it may occasionally be due to extension from some tuberculous bone of the cranium.

The process is most marked at the base of the brain, and the *gray tubercles*—which may easily escape observation—are seen in connection with the small arteries in the Sylvian and longitudinal fissures, and are for the most part deeply seated between the convolutions. A few scattered gray granulations are frequently visible on the upper surface of the hemispheres. The tubercles may be best seen by stripping off a piece of membrane containing a middle cerebral artery and its branches, spreading it out in water on a glass plate, and then examining it over a dark background (Fig. 209). The *tubercles* originate at those points in the walls of the small arteries of the pia mater where the bacilli

FIG. 209.

Tubercular meningitis. View of pia mater from the visceral side. *a*, *a′*, tubercles—single and aggregated; *b*, *b′*, folds of pia mater dipping between convolutions; *b′* to *d*, line of Sylvian fissure; *c*, dense mass of tubercles; *d*, single tubercles—many of these can be seen situated on the vessels which form a network over the individual convolutions. Natural size.

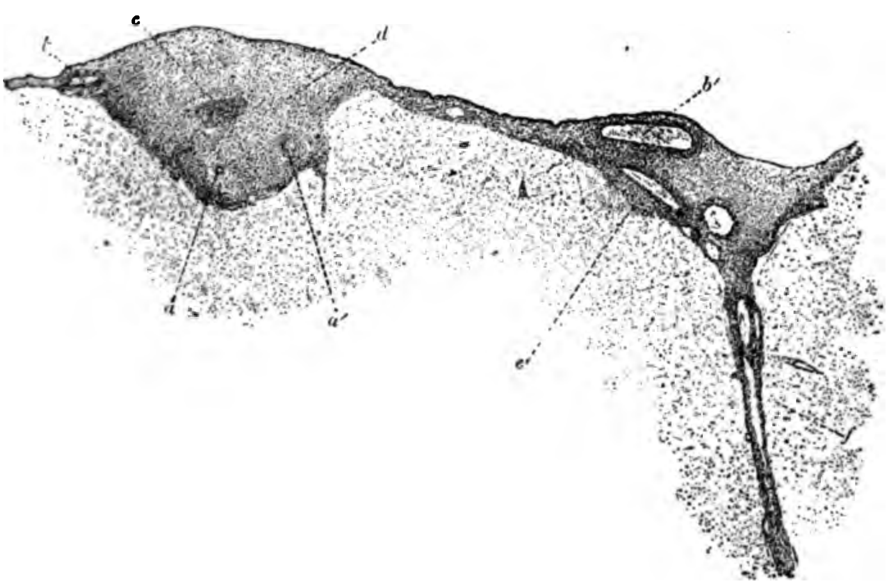
conveyed in the circulation happen to be arrested (Fig. 210). Thus, by the usual process of proliferation and infiltration, commencing at several centres, numerous small gray nodules are produced around the vessels and in the adjacent and surrounding lymphatics (p. 351). The tubercles thus formed rapidly caseate, though death usually occurs before this process is very advanced.

Thrombosis may occur in the affected vessels, or these may rupture, causing minute extravasations of blood. A *fibrinous inflammatory exudation* takes place, and the meshes of the pia mater become infiltrated

with a serofibrinous or puriform liquid, which tends to collect in the grooves between the convolutions, especially at the base of the brain. The subarachnoid fluid is turbid and increased in quantity, while the pressure within the dura mater rises steadily.

These changes in the pia mater at the base of the brain are attended by hyperæmia, infiltration with leucocytes and fluid, and slight softening of the subjacent cortical substance, accounting for the early delirium and hyperæsthesia of the special senses. The ependyma and choroid plexus also become hyperæmic, and may be covered with inflammatory exudation; while the walls of the ventricles, the fornix, and the soft commissure, *soften*. The lateral ventricles become progressively *distended* with fluid (*acute hydrocephalus*), so that the convolutions on the surface of the hemispheres are found pressed against the skull and *flattened*. It is uncertain how far this fluid is due to local inflammatory exudation, and how far to dropsy, since the exudation generally causes marked pressure upon the veins of Galen near their entry into the straight sinus. All trace of fluid is driven from the subdural space, and the arachnoid is dry and sticky.

FIG. 210.



Tuberculosis of pia mater. Showing a wedge-shaped tubercle, with inflammation of pia mater, and cellular infiltration of cerebral cortex. *a*, *a'*, giant-cells; *b*, *b'*, arteries in pia mater; *c*, caseating patch at centre of tubercle (*d*); *e*, eruption of cells from pia mater, marking commencement of another tubercle; *f*, fold of pia mater between convolutions. × 25.

Insensibility deepening into coma precedes death. This is due to the direct effect of the rise in intracranial pressure on the cells of the cerebral centres, and to the injury caused by the inflammatory process to which they are subjected.

Tuberculous Masses in the Brain.—Large masses of conglomerate tubercle (p. 351) are occasionally met with in the brain, unassociated at first with any general tubercular process. They are due to the local growth of one or more tubercle-bacilli carried to, and arrested in, one of the small terminal arteries. No bacilli are conveyed from this focus to any distant point and the growth remains a strictly local one. The masses, which vary in size from a pea to a hazel-nut or even to a hen's egg, commonly occur in the cerebral substance, especially at the base of the brain. They are of a pale yellow color and firm consistence, and usually form round globular tumors. Their surface is often seen to be covered with minute gray nodules, which extend into the surrounding tissue; and, on section, similar nodules are sometimes visible, scattered through the substance of the tumor. In most cases only one or two such masses are found, but occasionally they are more numerous. They occur especially in childhood. Near the edge, where the structure of the tubercles is recognizable and typical, compressed or obliterated blood-vessels may be seen. These masses are infective, and not infrequently lead, after an interval of some months or years, to tubercular meningitis or to general miliary tuberculosis.

Tuberculosis of Lymphatic Glands.

In the lymphatic glands, tubercular processes first give rise to changes in the cortical portions, inasmuch as it is to these that the infective material, brought by the lymphatic vessels, is first conveyed (Fig. 211). In the earlier stage of the process small pale gray nodules are often visible scattered through the cortex. They gradually increase in size and become caseous. The gland meanwhile enlarges from the addition to its substance of these "tubercles," which gradually spread in along the lymph-sinuses to the medullary portion.

By this time the distinction between the medullary and cortical portions is lost, in consequence of the infiltration and filling up of the lymph-sinuses. A section at this stage presents a grayish homogeneous surface, on which are patches of caseous material. Fibroid changes frequently follow, and the capsule thickens, so that the caseous masses may become surrounded by dense fibrous tissue. The whole gland, especially in children, may be rapidly converted into a caseous mass. The caseous portions may subsequently soften, dry up, or calcify (p. 351).

Sometimes no "tubercles" are visible to the naked eye, though a section in the early stage has a pulpy, swollen appearance, and may be distinctly more vascular than normal. Microscopically, small foci, consisting of epithelioid cells surrounded by leucocytes, are found. These may persist unchanged for some years and then disappear, or caseation and fibroid changes may ultimately supervene.

As before stated, the affection of lymphatic glands is, in most cases, secondary to a tubercular inflammation in the area whence they draw

their lymph; but sometimes it *appears* to be primary, bacilli having entered through the mucous membrane or skin without exciting any

Fig. 211.

Tuberculous lymphatic gland: *a*, thickened capsule of gland; *b*, *b*, caseous areas; *c*, *c*, giant-cells surrounded by inflammatory zone.

inflammation at the seat of invasion. The glands most commonly affected are the cervical, bronchial, and mesenteric.

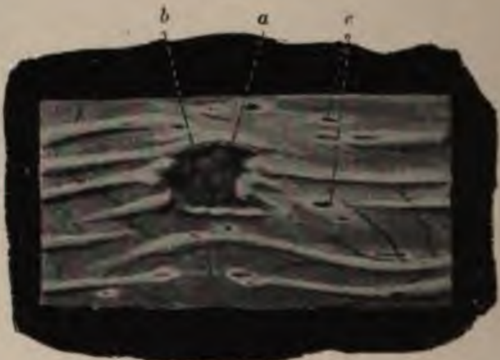
Tuberculosis of the Alimentary Tract.

The alimentary tract is a common seat of tuberculosis; it is, moreover, extremely probable that some catarrhal affections of the tonsils and pharynx, of the Eustachian tube and middle ear, as well as of the intestine, are due to the growth of tubercle-bacilli.

Tubercular ulceration or fissure of the lip, usually with marked thickening, is not uncommon in children and young adults. On the tongue and pharynx tubercular ulceration is rare, and is usually secon-

dary—at least in point of time—to pulmonary tuberculosis. The occurrence of tubercles in the œsophagus and stomach is very rare, but cases have been described. The course and appearances (microscopic and naked-eye) of all these ulcers are the same. They will be described in

FIG. 212.



Tuberculosis of intestine. *a*, Tubercles projecting from the floor of a tubercular ulcer; *b*, slightly thickened edge of ulcer; *c*, ulceration of solitary lymphoid follicles. Natural size.

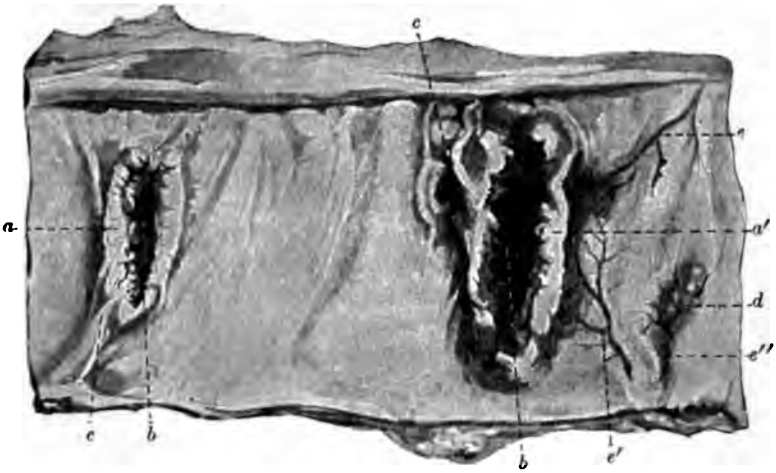
the next section, as the intestine is the part of the alimentary tract in which they are most frequently found.

Tuberculosis of Intestine.—Primary tuberculosis of the intestine is rare in adults. It is probably caused by infection from tuberculous milk or meat. Secondary infection of the intestine occurs in from half to two-thirds of the fatal cases of phthisis, and is caused by swallowed tuberculous sputum. The small and the large intestine are said to be affected with about equal frequency, and *both* are generally involved. The morbid process begins in the solitary (Fig. 212) and agminated follicles (Fig. 213), and is most marked where these are most numerous, namely, at the lower end of the ileum and in the cæcum; but any part may be affected.

The first stage of the process consists in the appearance of tubercles in some solitary glands and in certain follicles (not all) of some Peyer's patches. The affected lymphoid tissue swells, and therefore projects above the surface. The new elements, consisting largely of leucocytes, then undergo fatty changes and soften. The degeneration in Peyer's patches, commencing at a number of separate centres, is followed by a patchy ulceration of the mucous membrane; and the process extends by the development and subsequent breaking down of fresh tubercles at the margin, until a considerable part of the patch is destroyed. As the result of these changes an ulcerated surface is produced, the floor and edges of which are more or less thickened, owing to the production of tubercles in the surrounding tissues (Fig. 213). In the floor of the ulcer, formed usually by the submucous, sometimes by the muscular, and rarely by the peritoneal coat, small tubercles are developed, prin-

cipally in connection with the bloodvessels and lymphatics, and as these are arranged transversely around the intestine, the infiltration

FIG. 213.



Tubercular ulceration of ileum (interior). Two ulcers with long axes at right angles to that of intestine. *a*, *a'*, thickened shelving walls of ulcers, containing tubercles; *b*, *b'*, roughened floor, with tubercular nodules and small sloughs; *c*, *c'*, outlying thickening due to tubercular infiltration; *d*, a mass of recent gray tubercles around a vessel *e''*; *e*, *e'*, *e''*, dilated vessels in neighborhood of large ulcer. Natural size.

proceeds in the same direction. These nodules also soften and become caseous, and thus the process of ulceration gradually extends trans-

FIG. 214.

Tubercular ulceration of ileum (exterior). *a*, floor and walls of ulcer as seen on peritoneal side; *b*, outlying tubercular infiltration; *c*, subperitoneal vessels. Natural size.

versely until a complete ring of the mucous membrane may be destroyed (*annular ulcer*). The presence of tubercles on the peritoneal surface,

together with the dilatation of the neighboring vessels, may reveal the position of the ulcers before the bowel is opened (Fig. 214). By the blending of adjacent ulcers the mucous membrane is cut up into irregular patches; and, in extensive cases, only a few islets and bands are left in wide areas of the bowel. The ulcers thus produced (Fig. 215) present a strong contrast to those of typhoid fever (Fig. 216). Tubercle-

Fig. 215.

A tubercular ulcer of the intestine (diagrammatic). *a*, mucous membrane; *b*, submucous tissue; *c*, muscular coat; *d*, peritoneum.

Fig. 216.

A typhoid ulcer of the intestine (diagrammatic), showing the undermined edges of the ulcer and the slough still adherent. *a*, mucous membrane; *b*, submucous tissue; *c*, muscular coat; *d*, peritoneum.

bacilli are usually numerous and may be recognized in the stools by suitable staining.

Tubercular ulcers rarely, if ever, heal; but an ulcer *may* heal at one place, while it spreads at another, and the contraction of any resulting scar-tissue leads to marked stricture of the gut, and occasionally to complete obstruction. Owing to the thickening of the tissues at its base, perforation is an exceptional occurrence. This may take place into a neighboring viscus to which the ulcer has become adherent, or into the peritoneal cavity.

The lymphatic glands in connection with tubercular ulcers are generally affected. The lacteals leading from the ulcers, and even the thoracic duct itself, may be irregularly swollen by tubercles in their walls.

Tubercular disease of the peritoneum is considered in the section dealing with Inflammation of Serous Membranes.

Tuberculosis of Bones and Joints.

These parts may be conveniently taken together, as tubercular disease of a joint is frequently secondary to similar disease of a bone, and *vice versâ*. The primary disease is, of course, due to infection through the blood; the secondary, to extension from the primary focus.

In cases of acute general tuberculosis, both bones and joints may be the seats of *miliary tubercles*. In *bones*, the tubercles are found chiefly in cancellous parts; in *joints*, in the synovial and subsynovial tissue. They present no peculiarities and cause no local symptoms. It is said that miliary tubercles may be scattered through a bone without any general tuberculosis being present; and certainly multiple foci are not uncommon in the synovial membrane of a single joint.

Tubercular Periostitis and Osteomyelitis.—Periostitis and osteomyelitis, when due to "tubercle," often coexist, as when caused by other irritants. *Periostitis* cannot exist without a superficial *osteitis*; but the

converse is not true, for a deep bony focus of tubercular inflammation may be present without any obvious involvement of the periosteum.

Seats.—Among the bones which are affected primarily are the bodies of the vertebræ, the ends of the long bones, the bones of the carpus and tarsus, the phalanges, and less often the metacarpal and metatarsal bones and the ribs. The shafts of the typical long bones are rarely affected by tubercular processes. The same may be said of the cranial bones; but certain bones of the face not uncommonly suffer.

The tubercular process more often starts in the bone than in the periosteum. Periosteal changes occasionally predominate in the case of the ribs, phalanges, and bodies of the vertebræ: when this is the case, early abscess almost always leads to their recognition. But in the vertebræ, and probably in the phalanges, primary central changes are much the commoner.

Morbid Changes.—Bacilli are deposited at a certain spot, *e. g.*, in an epiphysis. Miliary tubercles next develop: a group of these becomes surrounded by a mass of granulation-tissue; and this again, in cases which are not progressing rapidly, and where irritation is not intense, by a zone of fibrous tissue. In this outer zone it is common to find the bony trabeculæ becoming thicker at the expense of the spaces—*i. e.*, the bone becoming sclerosed; more centrally, in the area of greater irritation, the trabeculæ are undergoing absorption.

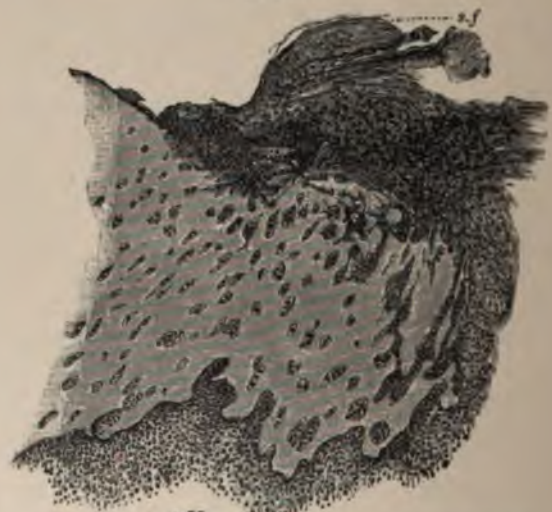
Bacilli carried from the primary focus cause infection of the surrounding tissue and the formation of tubercles in the granulation-tissue zone. As these increase in number they gradually blend with the parent mass, which meanwhile has probably undergone caseation. The granulation-zone in the meantime extends into and replaces the zone of fibrous tissue and of bony sclerosis, which in its turn reappears still farther from the centre. Thus the process spreads—now quickly, now slowly. Cure may be effected by the encapsulation of the caseous masses in fibrous tissue. This is sometimes followed by their calcification. On the other hand, the disease may spread till the surface of the bone is reached and the soft parts have become infected. Any portion of bone separated entire by surrounding caseation forms a *sequestrum*. Usually only small fragments of trabeculæ are thus separated; but sometimes caseation follows infiltration so rapidly that masses of bone as large as a filbert, or even larger, are detached. A whole epiphysis, such as the head of the femur, may thus die. As Cheyne has stated, the trabeculæ of the sequestra are often thickened, showing that a chronic inflammation preceded the change which caused the necrosis. This effectually disposes of König's hypothesis that the sequestra (which for some reason are often wedge-shaped) are due to embolism. Sometimes the sequestra are soft and crumbling, consisting of rarefied bone; sometimes the contents of the spaces, thus enlarged by rarefying osteitis, are calcified. An abscess often forms with or without necrosis.

When the periosteum is primarily affected, the enlargement of the bone soon becomes apparent, owing to the growth of tubercles imbedded in inflammatory tissue in the deeper layers of the periosteum and in

the superficial Haversian canals. This growth may extend over a wide area of bone, or may penetrate deeply at one or more spots, eroding the bone as it grows, even after causing a preliminary sclerosis. Commonly an abscess forms, and bursts if not opened. The rough surface of the infiltrated bone is then exposed. The resulting space is filled with a milk-like fluid, often containing caseating masses and bits of bone. The wall of such an abscess is formed of dense fibrous tissue lined by a layer of granulation-tissue which can be easily detached (p. 174).

On section, this wall shows, from without inward, œdematous fibroid tissue, probably containing tubercles with central giant-cells; then granulation-tissue with numerous but less typical tubercles; and, lastly, a layer, chiefly of epithelioid cells, which becomes more and more caseous as the cavity is approached. The extent to which a chronic abscess arising from tubercular disease of the vertebræ (Pott's disease) may burrow through the tissues, has already been described.

Fig. 217.



Edge of cartilage of knee in tubercular arthritis, resting upon inflamed bone, and markedly eroded on this aspect. The free surface of the cartilage is overgrown by a soft synovial fold (s. f.). Several channels, by means of which cells have reached the capsules of cartilage cells, have been laid open. × 55. (F. T. Paul.)

Tuberculosis of Cartilage.—Hyaline cartilage, being a nonvascular tissue, is never attacked primarily. Destruction of cartilage is sometimes due to the *spread inward*, over the surface of the cartilage, of tuberculous outgrowths from the synovial membrane: these processes adhere like ivy, and gradually erode the cartilage, producing a cribriform appearance (Fig. 217). Similar destruction may also be due to the *perforation* of the cartilage by a mass of tuberculous tissue sprouting through it from a focus in the subjacent bone; or to the *spreading*

beneath the cartilage of similar tissue from a bony source. Large pieces of cartilage may thus be loosened from the bone, while still retaining a normal appearance on the side toward the joint. In one or other of the above ways túbercular caries of the surfaces of a joint is established.

Tuberculosis of Synovial Membranes.—The tubercular changes met with in the synovial membrane are the following: (1) *acute miliary tuberculosis*, as mentioned above; (2) *diffuse thickening* (*tumor albus*)—by far the most frequent and important condition; (3) *nodular thickening* (*synovitis tuberosa*); (4) *serous effusion* or *hydrops*; and (5) *suppurative inflammation* or *empyema*.

Diffuse thickening may be primary or secondary. When *primary*, it is due to the settlement of bacilli at one or more spots in the synovial or subsynovial tissue. Tuberculous masses grow and spread, while the surrounding tissues become more or less swollen and gelatinous-looking from œdema and cell-infiltration. Clear or puriform fluid may be effused into the joint. The tuberculous foci may soften and open either into the joint or into the periarticular tissues, or may form an abscess in the thickened synovial membrane. When *secondary*, the diffuse thickening may be due to bursting of a focus from the bone into the joint, and infection of the whole synovial membrane from within. Soon afterward this membrane presents the structure of the wall of a chronic abscess, and its cavity probably contains turbid or puriform fluid. In other cases the thickening may be due chiefly to œdema of the synovial membrane excited by the presence of a focus in the bone, which has reached the surface at the reflection of the synovial membrane, and has thus been shut off from the cavity of the joint. At this point of reflection the membrane becomes infected, and the tuberculous process leads to much œdema of the neighboring parts. Cheyne states that in such cases he has been unable to discover any evidence of infection in the œdematous synovial membrane at a distance from the focus—a point of much practical importance.

In *synovitis tuberosa*, fungous masses of tubercular structure, from the size of a chestnut downward, hang in greater or smaller numbers from the synovial membrane into the joint, which almost always contains fluid: this is often blood-stained. The membrane may be thick and deeply blood-stained toward the joint. The disease is due to infection conveyed by the blood. Secondary infection from the diseased membrane is unusual.

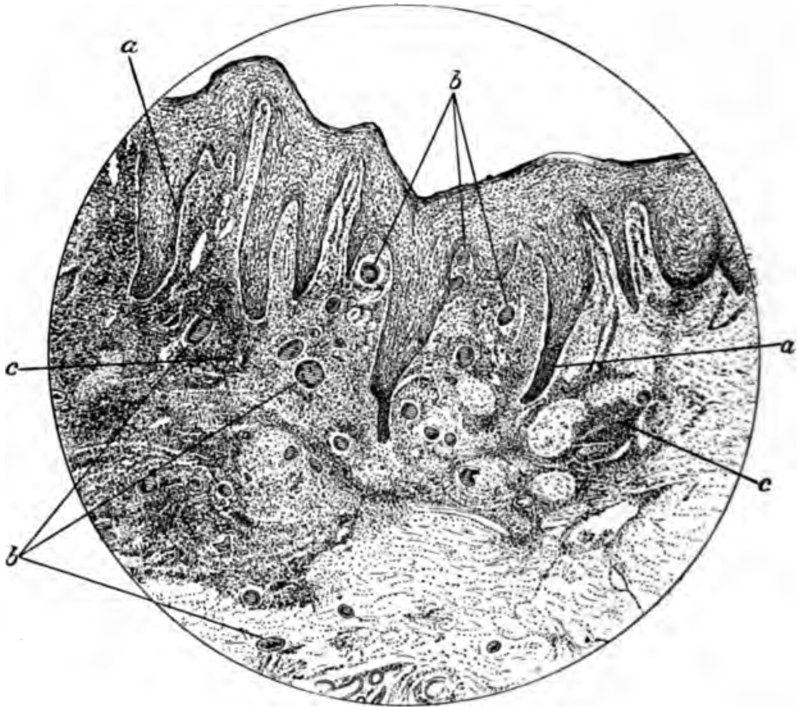
Effusion may take place before thickening of the synovial membrane begins (*tubercular hydrops*), and is indistinguishable at this stage from simple synovial effusion. König states that in early stages a thin layer of tuberculous tissue can be found on the surface toward the joint.

Purulent effusion (*tubercular empyema of the joint*) is indistinguishable from tubercular hydrops until the fluid is drawn off: it occurs in old people and in highly tubercular subjects.

Tuberculosis of the Skin.

Tuberculosis of the skin gives rise to many varieties of inflammation, of which some tend to suppurate. These are generally grouped under the term **Scrofuloderma** (*tuberculides*).

FIG. 218.



Lupus vulgaris. *a, a*, epithelial down-growths; *b, b*, giant-cells; *c, c*, inflammatory infiltration × 200. (From a specimen by Dr. J. M. H. MacLeod.)

Lupus vulgaris is a form of tuberculosis characterized by the appearance of reddish-brown nodules of granulation-tissue upon the *skin* (chiefly of the face), and much less commonly upon the *mucous membranes* of the conjunctiva, pharynx, vulva, and vagina. The nodules are situated primarily in the corium, and at first are smaller than a pin's head, though they may reach the size of a pea; these blend to form a more or less diffuse mass, while fresh foci appear at the periphery. The disease generally *appears* between the age of two years and puberty, and is especially common in those suffering from chronic tuberculosis in other parts of the body: *recurrences* may take place again and again, and the disease may thus last, off and on, throughout a lifetime.

Microscopically, the nodules consist of granulation-tissue containing epithelioid cells and often a good many giant-cells. Many of them

differ from true tubercles in being *rather richly vascular*. The intercellular substance is scanty and homogeneous. It is not uncommon to find that long anastomosing processes of epithelium have grown down into the round-celled growth. There is almost invariably increase in the size of the interpapillary downgrowths of epithelium (Fig. 218).

The disease spreads by the production of fresh nodules at the margin of the primary focus. Its course is always chronic, and when the patch has reached a certain size it may remain quiescent. The nodules and infiltration may end in degeneration and *absorption*—a white scar being left—or in *ulceration*. After eating away the tissues to varying depths, sometimes destroying large portions of the nose, lip, or eyelid, the ulcers may heal; or healing may go on at one point and destruction at another. There is little or no tendency to caseation, and glands rarely become affected. Most of those suffering from lupus die of tuberculosis of some other part.

Ætiology.—The tubercular origin of this disease is established on the following grounds: (1) tubercle-bacilli are found in the affected tissues; (2) pure cultures of tubercle-bacilli can be obtained from such tissues; (3) the inoculation of these cultures, or of the lupus-tissue itself, gives rise to tuberculosis; (4) injection of tuberculin is followed by an inflammatory reaction in lupus-tissues; (5) the structure of the tissue is such as would result from the very gradual growth of the tubercle-bacillus; (6) the temperature of the skin of the face is only a little above the lowest limit at which the bacillus will grow; and (7) there is in many cases of lupus a strong probability in favor of accidental inoculation with tubercle-bacillus.

Scrofula.

A constitutional condition known as *Scrofula* was formerly described, and said to be characterized by a liability of certain tissues to become the seat of chronic inflammation. This susceptibility was said to be most marked in mucous membranes, lymphatic glands, skin, bones, and joints. The cases so described are now known to have been due either to chronic tuberculosis, or to the infection of weakly individuals with some other pathogenic organisms. Many of the latter class ultimately die of tuberculosis.

LEPROSY.

Leprosy is a chronic, progressive, infective disease due to the introduction of the Bacillus lepræ and its growth in the tissues.

There are two chief varieties, *nodular*[1] and *anæsthetic*. In the former, the lesions affect chiefly the skin; in the latter, chiefly the nerves. The appearance of these changes is preceded by an incubation and a prodromal period. These together extend over nearly five years, and are often followed by a series of successive skin-eruptions.

In **nodular** leprosy patches of hyperæmia are followed by thicken-

[1] This variety is often called "tubercular." The term is objectionable, as it suggests an association with the tubercle-bacillus.

ing of the skin with the formation of small flat nodules, which grow very gradually and often run together, until, in some cases, they reach the size of walnuts. These changes are especially developed on parts exposed to the air—face, hands, and feet—and appear sometimes singly, sometimes in groups. The affected skin is at first firm and red or brownish; later on it becomes soft and pale: unless injured, it rarely ulcerates until some years have elapsed (Fig. 219). When ulcers do

Fig. 219.

Nodular leprosy. (Ziegler, after G. Münch.)

form they cause great destruction of features and other parts (*lepra mutilans*). Healing may occur here and there. The nodules may affect other parts of the body, especially the extensor aspects of the limbs, and the mucous membranes of the eye, nose, mouth, and larynx.

In **anæsthetic** leprosy, cylindrical or fusiform swellings occur upon nerves, especially the ulnar and external popliteal, and the usual results of neuritis follow. These swellings surround long portions of the nerves, affecting primarily the cutaneous and, later, the muscular branches. At first the skin is often painful and hyperæsthetic; later on it becomes thin, pale, and insensitive, while the paralyzed muscles waste. A bullous eruption (*pemphigus leprosus*) in the area of an affected nerve may be the first sign of the disease; these bullæ may either dry up, leaving pale insensitive patches with a pigmented border, or they may be followed at once by ulcers. Sooner or later ulcers

form upon the anæsthetic parts, leading to extensive destruction and even to dropping off of fingers, toes, or of large portions of limbs (*lepra mutilans*).

The two forms may run their course separately, but often occur together. The anæsthetic variety occurs chiefly in hot climates. In each form the glands receiving lymph from the diseased parts enlarge—first the superficial ones, then the deeper. Viscera—especially the liver, spleen, and testes—may also be enlarged. In the nodular form death results from exhaustion or some intercurrent disease, after a course of eight or ten years; in the anæsthetic form the duration is about twice as long.

FIG. 220.

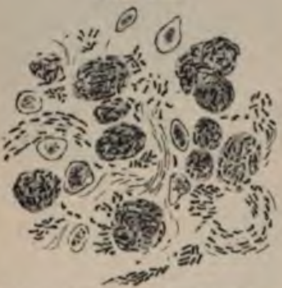
Leprous nodule. Section through the skin. The dark masses consist of bacilli closely packed together. × 120. (From a specimen by Dr. J. M. H. MacLeod.)

Histology.—To the **naked eye** the new tissue, wherever situated, has a grayish or yellowish semi-transparent, homogeneous appearance. The loose areolar tissues are chiefly affected, and, in a less degree, lymphoid tissue. **Microscopically**, the nodules consist of granulation tissue with large numbers of bacilli (Fig. 220). Prominent in the new tissue are numerous large, granular, vacuolated, cell-like masses known

as *lepra-cells* (Fig. 221); the vacuoles contain masses of bacilli. These cells are frequently found in the lymph-spaces.

According to the old view, lepra-cells are epithelioid cells, possibly derived from the endothelium lining the lymph-spaces; while the vacuoles are the intracellular excretory products of the enclosed bacilli. According to Bergengrün and other recent observers, a lepra-cell is a transverse section of a lymphatic stuffed with bacilli which have led to coagulation of the contained lymph—a lymphatic thrombus. The irritation caused by these thrombi gives rise to proliferation of the lining endothelium, and from this are formed the giant-cells, which in leprosy do not commonly contain bacilli.

FIG. 221.



Leprous nodule. Portion of preceding figure highly magnified, showing bacilli lying in "lepra-cells" and in lymphatic channels. × 750.

The fusiform swellings on the nerves consist of degenerated nerve fibres and proliferated connective tissue with numerous bacilli contained within the cells or lying free in the new tissue.

The new tissue in the *skin* very gradually undergoes fatty degeneration and is absorbed, or breaks down. The foci run together, and the diseased part appears, on section, to be divided into nodular masses by fibrous bands. Other tissues may, on account of the interference with their nutrition, necrose or atrophy.

The *lymphatic glands* contain small fibrous patches. As Delépine points out, the *liver*, *spleen* and *nerves* all show signs of chronic interstitial inflammation. The *lungs* are often said to be tuberculous. They certainly have the appearances of organs undergoing caseous broncho-pneumonia; but it is doubtful whether this condition is not frequently due to the leprosy-bacillus, although tuberculosis is unquestionably common in lepers.

Etiology.—This disease is endemic in many parts of the world, especially in the East and West Indies, China, South America, and Equatorial and Southern Africa. From the fourth to the fourteenth century it was widely spread over Europe, but began to die away at the beginning of the fifteenth, and was nearly extinct by the end of that century, when syphilis first became prominent. Leprosy still lingers in many places in Europe, particularly in Norway, Sweden, and Iceland.

From time immemorial leprosy has been looked upon as a contagious disease, and lepers have been rigorously excluded from social communities. In many cases, however, lepers have been known to live in the closest association with healthy people without communicating the disease. On the other hand, no one ever contracts the disease without having been brought into contact with the contagium, which may in all probability remain latent for years. The extremely

gradual development of the disease renders its contagiousness difficult to prove.

It may be noted that leprosy flourishes in all climates and upon all soils. There is no evidence that poor diet and salt fish take any prominent part in its causation, as some have thought; or that the disease is hereditary, although Hirsch strongly maintained that it was. Possibly there may be some hereditary predisposition analogous to that believed to exist in the case of phthisis.

Observers are agreed that there is constantly present in all the recent primary lesions of leprosy a bacillus very closely resembling in its characters the tubercle-bacillus (p. 343).

The bacilli found in leprosy may vary in shape, size, and staining affinities. Delépine showed that in one case the bacilli free in the tissues were shorter and more readily stained than those in the lepra-cells; while those in the skin and mucous membranes were longer and more rapidly stained than those in the liver and spleen. The bacilli may generally be distinguished from tubercle-bacilli as seen in human tissues, by their enormous numbers, and by their occurrence in the lymphatics and in the tissues. Moreover, giant-cells are less common, and do not often contain bacilli.

Attempts to cultivate the organism have so generally failed that the few recorded exceptions are of little value until more fully confirmed. Amid conditions under which the tubercle-bacillus will flourish, the leprosy-bacillus will not even grow at all.

Nor do inoculation-experiments give decisive results. In the case of a criminal, to whom inoculation had been offered as an alternative to execution, the disease followed the inoculation, but the result was inconclusive, as the man had up to that time been in frequent contact with lepers. Whether the affected tissues be introduced into other parts of leprous patients, or into animals, the results are uniformly unsuccessful, though the bacilli themselves are not destroyed, for they can be found months afterward in the tissues.

SYPHILIS.

The disease known as *syphilis* is characterized by the presence of inflammatory lesions occurring in foci, some of which are infective. The lesions thus possess some points of resemblance to those of tuberculosis and leprosy, but, on the other hand, in their seats, distributions, sequence, and histological characters, present certain peculiarities which make them characteristic of this disease. The primary lesion occurring at the point of inoculation is followed by enlargement of the neighboring lymphatic glands, and, later on, when the virus becomes generalized, by a series of changes in the skin and mucous membranes. At a still later period these may be succeeded by changes in the nervous system, bones, and internal organs—most of them the results of inflammatory processes induced by the syphilitic poison. Syphilis is a "chronic general infec-

tive disease," although the proof that it is due to any known organism is still incomplete.

I. Primary Lesion.—In all probability there is always a local lesion at the point of inoculation, though it may be exceedingly minute and not infrequently escape observation, especially in women. This primary lesion is a small hard nodule (*hard chancre*) in the skin or mucous membrane and consists of ordinary chronic inflammatory tissue, being made up of giant-cells, epithelioid cells, and a large proportion of leucocytes. There may also be some epithelial proliferation on its surface which is often eroded, a small ulcer with a hard base resulting. This ulcer may, of course, become infected with pyogenic cocci.

Columns of cells, probably leucocytes, extend from this indurated focus between the planes of connective tissue in the neighborhood, and, by means of lymphatics, reach the nearest lymph-glands. When the virus is introduced by absorption through a slight abrasion, a lymphatic can generally be found in the centre of the focus, and the infection spreads rapidly, by means of the connective-tissue spaces and lymphatics, to the glands, which are thus quickly involved, though no evidence of the generalization of the poison occurs for a period of time varying from two to six weeks. When accidentally inoculated, as in the course of an operation, the virus may gain direct entrance to the blood-stream and the evidence of general infection may thus occur much earlier, without any previous infection of the glands.

II. Secondary Lesions.—Two or three weeks after inoculation, lesions appear in many parts of the body as a result of the generalization of the virus. These are characterized by inflammation of the perivascular sheaths and adventitia of the smallest vessels, and by the presence of epithelioid cells and leucocytes. Many of the lesions are anatomically indistinguishable from simple inflammations of the same parts. The rashes, for example, are due to inflammatory hyperæmia with more or less infiltration of the superficial layer of the skin, enlargement of the papillæ, and, often, excessive epithelial multiplication (*mucous tubercles*). As a rule these inflammations end naturally in resolution; but, in tissues of feeble resisting power, ulceration may follow. Early syphilitic periostitis (*nodes*) is indistinguishable from traumatic inflammation, and syphilitic iritis is diagnosed from rheumatic iritis only by concomitant circumstances.

III. Tertiary Lesions.—Other lesions, sometimes known as *tertiary*, occur later. The most characteristic of these are **gummata**, but the most frequent is simple **fibroid induration.**

Fibroid Induration.—Anatomically, this is ordinary proliferative inflammation, ending in scar-tissue (p. 174). When the fibrous tissue is gradually developed without evidence of any change, except such degeneration and atrophy as may depend on or precede the subsequent contraction of this tissue, it is sometimes spoken of as an overgrowth of

connective tissue. The density of the new tissue varies in different cases and in different parts of the same organ. The infiltration *may* be general, but much more commonly the fibroid areas are separated by comparatively healthy portions of the organ. It is the *irregular distribution* of these lesions which makes them so *characteristic of syphilis.*

The *capsules* of organs are *irregularly thickened;* any serous coverings they may possess are involved, and more or less general adhesion to surrounding parts occurs. As the fibrous tissue contracts the organ shrinks and often becomes of stony hardness; but the irregular distribution of the exudation often causes unequal contraction and puckering of the surface, amounting in some cases to the formation of deep fissures which almost divide the organ into lobes. In these cases the diffuse growth has probably been combined with the gummatous, and the thickened capsule is connected with fibrous strands which extend deeply into the surrounding tissue.

The naked-eye examination of a testis which has undergone these changes shows adhesions between the layers of the tunica vaginalis, and intervening spaces containing fluid, as well as marked thickening of the tunica albuginea with dense bands of fibrous tissue extending from it toward the mediastinum. The natural reddish-brown color of the tubules is replaced by a much paler whitish-yellow tint, in which islands of normal tissue may remain. The consistence of the gland is greatly increased. One or two gummata may also be present. In syphilitic orchitis the affection of the tunica vaginalis is often proved during life by the presence of hydrocele.

When occurring in bone, this fibroid induration may ossify. Under the periosteum, it causes thickening of the bone. In the Haversian canals and cancellous spaces it leads to increase in density.

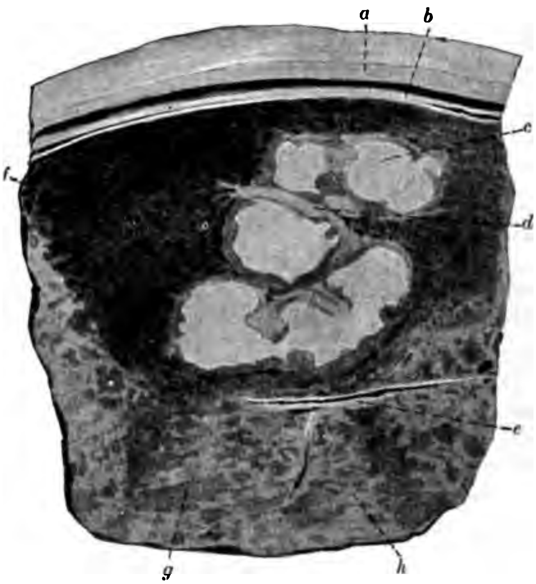
No definite distinction exists between fibroid induration and gummata. The former is practically a diffuse form of gummatous inflammation, and may perhaps be invariably preceded by the formation of gummata, of which it represents a final stage after all caseous matter has been absorbed.

Gummata. (*Syphilitic Tumors, Syphilomata.*)—As usually met with these are moderately firm yellowish-white nodules (Fig. 222). They vary in size from a hemp-seed to a walnut, and are surrounded by a zone of translucent fibrous-looking tissue, which sometimes has the appearance of a capsule, and which is so intimately associated with the surrounding structures that enucleation of the mass is impossible. The outline of the growth is generally irregular, owing to the number of fibrous processes which radiate from it along the natural septa of the organ (Fig. 223). In the *earlier* stages of their development, as seen in the liver in cases of congenital syphilis, where they occur as early secondary lesions, gummata are much softer in consistence, more vascular, and of a reddish-white color; whilst in their most *advanced* stages, owing to extensive degenerative changes, they may be opaque, yellow, and fatty.

Examined *microscopically*, gummata are found to vary in their minute structure according to their age. When recent they are

divisible into three zones. The *central* portions are composed of closely packed shrunken cells and nuclei, fat-granules and cholesterin, amongst which is generally a little fibrillated tissue. Surrounding this and directly continuous with it is the *intermediate* zone, consisting of epithelioid cells in a distinctly fibrillated matrix. The *peripheral* portion of the growth, which is in direct histological continuity with the surrounding structures, consists mainly of leucocytes, though epithelioid cells and even giant-cells are also found. Giant-cells are much rarer than in tuberculosis. The cells are separated by a scanty, homogeneous, intercellular material and numerous new bloodvessels. In older gum-

FIG. 222.



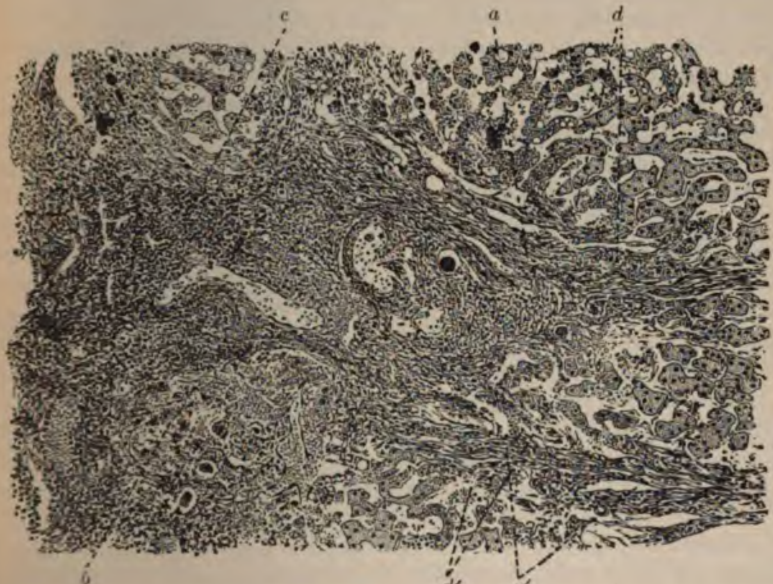
Gummata in the liver. *a*, diaphragm; *b*, peritoneum and capsule of liver; *c*, caseous masses; *d*, fibroid walls surrounding caseous masses; *e*, sublobular vein; *f*, *g*, areas undergoing amyloid degeneration; *h*, areas undergoing marked fatty changes. In this specimen the gummata are a short distance from the surface and no thickening of the capsule or puckering of the surface has occurred. Natural size.

mata, only two zones may be apparent, an *inner caseous* zone and an *outer fibrous* zone.

The origin of the cells in gummata is most likely the same as in tubercles. It seems probable, however, that the chemical effects of the syphilitic virus are less deadly to the life of the new cells than are the corresponding effects of the tubercular. The further development of the new tissue therefore proceeds, and vessels are formed. The caseation which next occurs is, in all probability, not so much due to the direct action of the virus as to the subsequent shutting off of the blood-supply. By means of changes, presently to be described, the walls of

the bloodvessels in the centre of a gumma become thickened, and in thickening, encroach upon and nearly obliterate the lumen. Subsequent thrombosis in the affected vessels completes the interference with the blood-stream. To these changes must also be added the strangulating effect on the bloodvessels, produced by the contraction of the new fibrous tissue. The parts thus gradually deprived of blood must degenerate, and this occurs at a comparatively early stage, although not so early as in tuberculosis. When the gumma is large, and particularly when the epithelioid cells are present in large numbers, the mass may be seen to be made up of an agglomeration of smaller growths, each having the characteristic structure. When the leucocytes predominate, the foci run

FIG. 223.



Edge of gumma of the liver. *a*, *a'*, fibrous strands extending into lobules of liver; *b*, fibrous wall of gumma, among which remnants of liver-cells are apparent (caseous mass lay to left of specimen and is not shown); *c*, masses of leucocytes; *d*, *d'*, liver-cells undergoing fatty changes in neighborhood of fibrous strands. × 120.

together and their outlines are lost. It has been recently stated that subcutaneous gummata originate in an *endophlebitis proliferans* followed by thrombosis, perivascular round-celled infiltration, and subsequent necrosis; and that in these cases *arterial* changes are not so constant.

In *early* stages, before they have produced marked destruction of tissue, gummata may disappear under treatment. In *later* stages their *central* fatty portions are frequently absorbed, leaving a radiating puckered scar; calcification is rare. If gummata become infected with pyogenic cocci, they soften and suppuration occurs around them; the

abscess bursts, and a yellow slough is exposed. This has a very characteristic appearance, resembling a piece of wet wash-leather: it is tough and coherent, unlike the dead tissue from the caseous centre of a tubercular focus. It gradually becomes detached, leaving a larger or smaller cavity with soft ragged margins. These changes can often be seen in the tongue. Gummata of the *skin* and *mucous membranes* are the most prone to take this course. These ulcerations must be distinguished from the superficial ulcerations connected with the early rashes. It seems probable that gummata may sometimes soften, just as tubercular nodules do, without the action of pyogenic cocci.

Gummata are met with in the skin and subcutaneous cellular tissue; in the submucous tissue, especially of the pharynx, soft palate, tongue, and larynx; in muscle, fasciæ, and bone; and in the connective tissue of organs—especially of the liver, brain, testicle, and kidney. Gummata also occur, but much less frequently, in the lungs, especially in *congenital* syphilis: simple localized fibroid indurations are found under the same circumstances.

No hard line can be drawn *clinically* or *pathologically* between secondary and tertiary lesions. In congenital syphilis, gummata and pericellular cirrhosis are among the earliest manifestations of the disease.

Contrast between Syphilitic and Tubercular Lesions.—Attention has previously been drawn to resemblances and distinctions between tubercular and syphilitic formations. The points of contrast may be thus summarized. In *syphilis*, (1) the contagion is more easily traceable; (2) the foci are larger, and show a greater tendency to organization, while endarteritis of their vessels is invariable; and (3) the lesions are always local, and pigmentation is common.

Parasyphilitic Lesions.—The name *parasyphilis* has been applied to certain affections of a degenerative nature, apparently due to the action of the syphilitic poison. The best known of these are tabes dorsalis (locomotor ataxy) and general paralysis of the insane. (See Diseases of the Nervous System.) The wasting of infants who are the subjects of congenital syphilis, but who present no evidence of gross organic disease and have not suffered from noticeable digestive derangements, may perhaps come under this heading.

Changes in Vessels.—Certain changes in the arteries, known as *Endarteritis obliterans*, occur in syphilis, either as a distinct local lesion—especially in the brain—or in conjunction with other syphilitic changes, as in gummata.

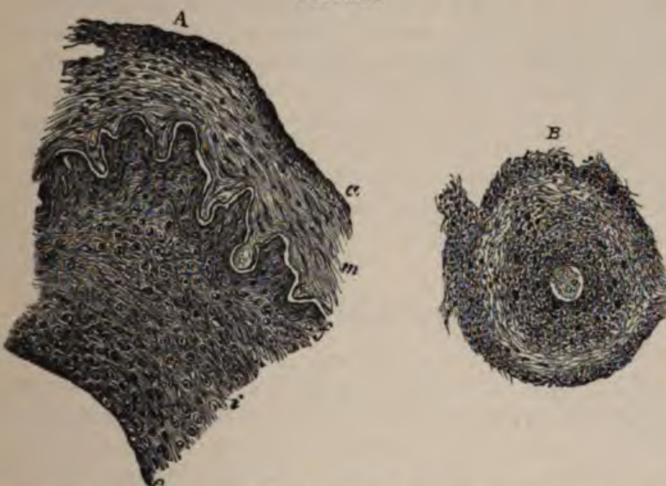
In the cerebral arteries the changes produce opacity and marked thickening of the vessel, with considerable diminution in its calibre. It is this diminution of the lumen of the vessel which is especially characteristic. The smaller vessels, arteries and veins, are chiefly affected, and their lumina may be quite obliterated.

When transverse sections of the vessels are examined microscopically, the changes are seen to be situated in the *inner* and *outer* coats (Fig. 224). The intima is considerably thickened by a cellular growth.

The growth, which is limited internally by the endothelium of the vessel, and externally by the membrana fenestrata, consists of chronic inflammatory tissue containing a large proportion of cells. Sometimes the elastic layer is split into several strands—a condition which gave rise to the opinion once held that a new elastic lamina was formed in syphilis.

In addition to this change in the intima, the outer coat is abnormally vascular and is infiltrated with small cells (Fig. 224), and to a less extent this cellular infiltration usually invades the muscular layer as well. The marked diminution of the lumen of the vessel and the

FIG. 224.



Syphilitic disease of cerebral arteries. A. Segment of middle cerebral artery, transverse section. *i*, thickened inner coat; *e*, endothelium; *f*, membrana fenestrata; *m*, muscular coat; *a*, adventitia. × 100. B. Small artery of pia mater, transverse section. Showing thickened inner coat, diminished lumen of vessel, and considerable infiltration of adventitia. The cavity of the vessel contains a clot. × 50.

consequent interference with the circulation, coupled with the changes in the endothelium, frequently lead to thrombosis, and consequently, when the cerebral vessels are affected, to *cerebral softening*.

Syphilis is one of the factors in the production of arterio-sclerosis and of aneurism. It also leads to amyloid degeneration of the walls of the vessels and other parts (p. 67).

Etiology.—Strong as is the *clinical* evidence of the infective nature of syphilis, nothing positive is known of its cause.

The poison exists in the primary sore, in mucous tubercles, and all secondary sores, and in the blood during the eruptive period, for all these are infective. Excision of the primary lesion does not prevent the development of the disease; probably because the infective agent has already reached the neighboring lymphatic glands. The virus is not present in normal secretions, such as milk, saliva, mucus, and

semen. The discharge from gummatous ulcers is usually not infective. Fibroid lesions are indications of the successful resistance of the tissues to the virus, and must be regarded as evidence of a healing process.

Klebs inoculated apes with portions of syphilitic tissue, and produced a disease closely resembling syphilis; and this experiment has been successfully repeated by Roux and Metchnikoff.

Many observers have described organisms which they have found in syphilitic lesions. None of these results have up to the present time been sufficiently confirmed. Lustgarten has described a bacillus very similar if not identical with that usually present in the smegma preputii.

Van Niessen obtained a coccus (*syphilococcus*) from a primary sore, cultivated it on gelatine and inoculated animals, thus producing hard sores and gummata. These results still need confirmation.

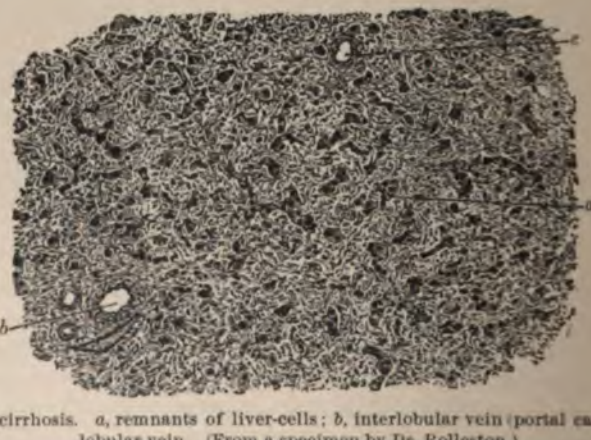
More recently De Lisle and Jullien have found polymorphic motile cocci in the blood of syphilitic patients. These cocci did not survive coagulation of the blood, in which process apparently some antagonistic body was liberated; they could be cultivated, however, if the blood were prevented from clotting. They were agglutinated by the serum of persons affected with syphilis.

Syphilitic Disease of the Liver.

The liver is one of the most frequent seats of syphilitic lesions.

In **adult life** the commonest change is the occurrence of caseous foci (gummata) imbedded in localized tracts of dense fibrous tissue, with processes radiating into the surrounding lobules of the liver, which is often undergoing fatty or amyloid degeneration (Fig. 223). These changes

Fig. 225.



Pericellular cirrhosis. *a*, remnants of liver-cells; *b*, interlobular vein (portal canal); *c*, intralobular vein. (From a specimen by Dr. Rolleston.)

are generally connected with fibroid thickening of the capsule and adjacent peritoneum. The softening of gummatous masses may give rise

to large abscess-cavities with thick fibrous walls. Sometimes no caseous masses may be found, and the change is limited to scar-like depressions on the surface of the liver, which is irregularly and deeply puckered. In these cases it is possible that there may have been gummata which have since been absorbed. In other cases, as Adami points out, a more uniform pericellular cirrhosis occurs and persists. This involves the central portions of the lobules quite as much as the peripheral.

In **congenital** syphilis two changes are common: (1) Recent gummata, consisting of small, pale, somewhat ill-defined patches of granulation-tissue, are not infrequently met with. (2) More often, diffuse changes, resulting in pericellular cirrhosis, are found (see Pericellular Cirrhosis of Liver). According to Hecker, the cellular accumulations causing the enlargement of the liver so common in children born with syphilis are made up partly of proliferated liver-cells and partly of cells suggestive of newly formed red corpuscles. Hecker accordingly suggests that the condition of the liver is due to a continuation and excess of the normal fœtal processes in that organ.

Amyloid disease may be found in the liver as a local change in the neighborhood of gummata (Fig. 222); it may also result from syphilis apart from any of the above changes.

It is unnecessary to describe the syphilitic lesions which occur in other organs, as they all present the same general characters—viz., cell-infiltrations, scars, fibroid indurations, and gummata, singly, or in combination. The late syphilitic affections of the central nervous system have already been alluded to, and are more fully discussed in Chapter XIII.

GLANDERS.

Glanders (*equinia*), an infective disease, due to the growth of the *Bacillus mallei*, is, like tuberculosis and syphilis, distinguished by the presence of characteristic local lesions.

In *animals* two varieties of the disease are described. In (1) *glanders*, the nasal mucous membrane and its prolongations are the seat of the earliest lesions; in (2) *farcy*, the skin and subcutaneous tissue. Each form may run a rapid or a slow course. Both varieties of the disease are common among equine animals, especially horses, and are communicable from them to other animals, including man, though this happens but rarely. The disease is also transferable from man to man.

In *man* the distinction between the two varieties does not obtain, as the lesions of the one form nearly always supervene upon those of the other. In view of the very fatal character of glanders contracted by infection with laboratory cultures of the organisms, and, on the other hand, of the comparative rarity of infection from horses, it would seem that the bacilli are to some extent attenuated by passage through this animal, or at least rendered less adapted to a human environment.

Appearances.—The characteristic lesions resemble acute abscesses in some particulars, and typical tubercles in others. They are best seen in the more **chronic** varieties. A circumscribed nodule (*farcy-bud*) appears, varying in size from a mere point to that of a pea or bean. On section, this is found to consist of a mass of leucocytes in the centre and a zone of epithelioid cells around it, while an additional external zone of red blood-corpuscles is not uncommon: vascularization of the bud is at best very imperfect. Necrosis occurs in the centre and more or less suppuration follows. When a farcy-bud forms near a free surface, an ulcer with a sharply cut indurated margin and a very foul base usually results. Such ulcers may heal, but their course is generally very chronic.

In the more **acute** forms of the disease the poison sets up ordinary suppuration at the spot where it develops. The inflammation is not always circumscribed: sometimes it is diffuse, giving rise to infiltration of muscles, subcutaneous tissue, and the connective tissue of the orbit. This is succeeded by suppuration at several points, or throughout the infiltrated tissue.

Course.—A wound is a common place of entry; mucous membranes, especially the conjunctival and nasal, are also seats of primary infection. In many cases there is no evidence to show how the poison has entered.

In **acute glanders**, after a variable period of incubation, inflammatory nodules appear in the mucous membrane of the nose, frontal

FIG. 226.

Section through a "bud" in the skin from a case of acute glanders. The horny layer has mostly disappeared and the Malpighian layer is pushed upward by the subjacent abscess (just below *a*). The mass of pus-corpuscles is just breaking down to form a cavity, the walls of which are infiltrated with similar cells. (Boyd.)

sinuses, or other places, and run on more or less rapidly to suppuration and ulceration. The fever and mucopurulent or bloody discharge from the nostrils are thus explained. The submaxillary and cervical glands swell—from infection through the lymphatics. The poison then enters the blood and is carried to distant parts, giving rise to metastatic inflammation in the lungs and other internal organs, in the

skin, and in the mucous membranes of the respiratory and alimentary tracts. Abscesses in the subcutaneous and intermuscular tissues are common, and suppuration in joints occurs. In fact, the disease resembles pyæmia in many respects, being, like it, due to the dissemination by the blood of an organism capable of exciting suppuration. The abscesses in organs are generally small, but may reach a large size. The respiratory and alimentary mucous membranes are probably infected from the nose. On the skin, red papules and larger patches of inflammation appear. On these, vesicles and then pustules—often with hemorrhagic contents—quickly develop. These constitute the rash of the disease. The earliest stage is a collection of round cells in the superficial part of a papilla; a little later a pustule is found to have developed under the rete. The fever is high throughout the disease, symptoms of prostration appear early, and death occurs with all the signs of septic poisoning.

In **chronic glanders** large "buds" appear in the subcutaneous, submucous, and intermuscular tissues. Those near the surface break down slowly, and form foul ulcers; the lymphatics become much swollen, hard, and knotted: and the glands are greatly enlarged. The general symptoms are much milder. This form often ends in recovery. In fatal cases the symptoms of acute glanders frequently supervene before death.

Etiology.—In the pus of abscesses in glanders, Schülz and Lœffler found slender rods, smaller than, but resembling generally, the bacilli of tuberculosis. Cultivated in the serum of horse's blood, these rods formed colonies, maintaining their initial form. After repeated cultivation, to ensure the absence of contamination, various animals were inoculated. The result varied with their susceptibility. In all, an indurated ulcer appeared at the site of inoculation; and curd-like lymphatics ran thence to swollen glands. In some, metastatic abscesses formed in internal organs; in others, death occurred rapidly, with symptoms of septic poisoning. In all, the above bacilli were found. Two horses were inoculated from a fourth cultivation: after some days' incubation the symptoms of glanders set in, and the older horse died in fourteen days. The other was extremely weak and was killed next day. The post-mortem signs were the same in both—viz., a sore the size of a twenty-five cent piece at the site of inoculation; hard and swollen lymphatics, leading from the sore to neighboring glands; abscesses in the lungs, from the size of a pea downward; farey-buds and ulcers studding the nasal mucosa.

By this one series of experiments the organism known as the *B. mallei* was proved to be the cause of glanders. The bacillus is non-motile, grows on ordinary media and potato, and does not form spores. It is apparently capable of existing outside the body for long periods in a virulent condition.

An extract of the cultures has been prepared, and is known as ***mallein.*** When injected subcutaneously in cases of glanders, it gives

rise to an inflammatory reaction at the seat of the disease and to a febrile reaction. In doubtful cases mallein is therefore injected as an aid to diagnosis, as it has comparatively slight effect, general or local, when injected into sound animals.

RHINOSCLEROMA.

This rare disease, which presents some points of resemblance to the foregoing, consists in the formation of hard, sharply defined masses in the skin or mucous membrane near the anterior nares, the process subsequently spreading to the lips, gums, nasal cavities, and thence to the palate. Later on, the pharnyx and glottis may be involved, thus becoming both rigid and narrowed. Similar changes have been described in the external auditory canals. The growth has never been known to generalize, and for years the health remains unaffected. When the disease is not interfered with, extension is slow but continuous. Recurrence has invariably and rapidly followed even apparently complete removal.

The masses round the nostril are like keloid or hypertrophic scars. They are light or dark brownish-red in color, and here and there smooth and fissured. The skin around is quite normal. There is little or no tendency to ulceration.

Microscopically, there is found dense infiltration of the corium with small round cells lying in a fibrillated stroma. Many of the cells are spindle-shaped, and a few may be epithelioid, but large cell-forms are the exception. The growth is moderately vascular and presents no tendency to fatty degeneration. Cornil describes some of the cells as containing "hyaline masses," which may also be present in the tissue.

Etiology.—The disease is regarded as infective on account of its morbid anatomy, coupled with the constant presence of a bacillus (Frisch). The bacilli are short and thick, ovoid, or even round, and two are often bound together in a capsule. The organism has been cultivated: it grows rapidly at 97° to 100° F. Inoculations with cultures or with pieces of the growth have been made in the noses of dogs, but have always failed. According to Mibelli, the "hyaline masses" consist of the "shed" capsules of the organisms.

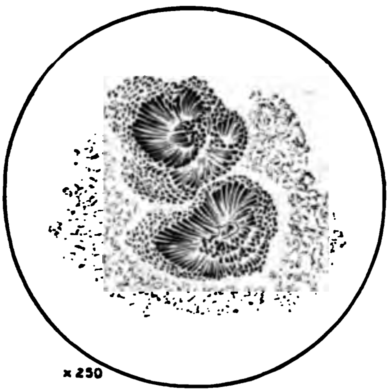
ACTINOMYCOSIS.

This disease consists in the formation of small sarcoma-like tumors or abscesses, due to the growth of a peculiar fungus—the *actinomyces*.[1] The commonest seats are the lung and liver, but the fungus may be found in any part. It is more commonly met with in the lower animals than in man. In cattle the disease most often affects the jaws.

[1] Greek, ἀκτίς, a ray; μύκης, a fungus.

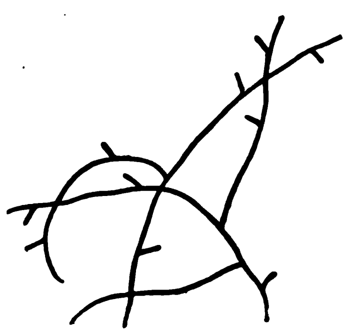
Appearances.—On section, the tumors have an open spongy appearance, and a puriform or caseous fluid can be squeezed from them. Besides fatty cells, this fluid contains many pale yellow granules, just large enough to be visible to the naked eye. These, when gently squeezed and cleared up by potash, are seen to consist of filaments radiating from a common centre, and bearing at their free ends club-shaped

FIG. 227.



Actinomyces. From the tongue of the ox. Two masses of club-shaped radiating filaments are seen. × 250.

FIG. 228.



Actinomyces hominis, showing true branching. × 1000.

swellings (Fig. 227). The filaments are often branched (Fig. 228) and frequently calcified. Threads and spherical bodies are found less frequently. The nodules and abscesses also contain granulation-tissue, intersected here and there by bands of fibrous tissue. In the older specimens there are found, round each fungus, the usual signs of a chronic inflammation caused by a slight, constant irritant (p. 173). The structure of the parasite is best seen when stained by Gram's method.

Etiology.—The fungus may enter by one of three channels.

1. **The Mouth.**—Through a carious tooth or extraction-wound the fungus reaches the interior of the jaw. It then grows and bursts through the outer plate, and gives rise to an abscess in the glands or in the connective tissue of the neck. It is probable that infection may also take place through the follicles of the tonsil in tonsillitis, or of the pharynx in pharyngitis (*prevertebral abscess*).

2. **The Respiratory Passages.**—When the fungus is inhaled, bronchial catarrh is set up, and the parasite may be found in the sputum. It next gains access to the alveolar walls and there gives rise to nodular foci. These develop into suppurating or caseous centres, which bear a superficial resemblance to the caseous bronchopneumonia of phthisis, but differ from it in being shut off from the healthy lung by a layer of healthy granulation-tissue, sometimes surrounded by dense fibrous tissue. The cavities may rapidly coalesce, with symptoms like those of phthisis,

though marked hæmoptysis is uncommon. Then, adhesions having formed over the diseased area, the fungus spreads to the posterior mediastinum, through the diaphragm into the peritoneum, liver, or spleen, or into the anterior mediastinum and pericardium. In this way the disease may give rise to peritonitis, abscess of liver or spleen, or pericarditis. Lastly, some of these abscesses, after much burrowing, may find their way to the surface of the chest-wall, involving the breast or even the subcutaneous tissue and skin. It is noteworthy that,

Fig. 229.

Actinomycosis of the liver. A large sponge-like area forms the centre of the specimen. This consists of dense fibrous trabeculæ enclosing small roundish spaces, filled up, in the recent state, with granulation-tissue and pus. The pus which escaped contained the minute yellow granules described in the text. Natural size.

though the actinomyces affects the lungs from above down, like the tubercle-bacillus, it leaves the apex—above the clavicle—uninvolved. The pleura and lung may occasionally be infected secondarily from the posterior mediastinum. In these cases the œsophagus is probably the source of infection. This disease, in its progress, may give rise to ordinary serous or purulent inflammations in which no trace of the actinomyces can be discovered.

3. The Intestine.—The intestine may be affected primarily from within, or, secondarily, by embolism or by extension from other organs. The primary form may lead merely to catarrh, but generally gives rise to nodular foci in the mucous and submucous tissues, which break down into ulcers with undermined edges. Perforation into the peritoneum, into other hollow viscera, or through the abdominal wall may result.

In many cases the channel of infection remains doubtful.

In exceptional cases actinomycotic embolism may lead to scattered abscesses accompanied by symptoms of pyæmia. Secondary foci may occur anywhere. Ponfick has seen a granulation-mass growing into the jugular vein in a case in which there were growths in the right auricle and ventricle.

For some time all attempts to cultivate the organism failed. This failure has been attributed to the fact that only the *club* forms were used, and that these are a degenerate form and incapable of cultivation. If the *threads* be taken, grayish crinkled colonies develop in about four weeks. The colonies thus obtained consist of *threads* and *spheres* (from transverse division of the threads), but *no clubs*. Inoculation of the cultures gives rise to the characteristic lesions, including the presence of both the *club* and *thread* forms of the parasite. The fungus belongs to the Streptothrix group—the members of which form branching threads (Fig. 228)—and is called *Streptothrix actinomyces*.

There is no reliable evidence that the disease can be acquired by direct infection from diseased meat. The history of an epidemic in Iceland suggests that the bristles from ears of barley and other cereals in penetrating the mucous membrane of the mouth and pharynx may give rise to the disease, though it is not yet proved that the parasite can flourish in the ears of cereals.

Madura Foot or Myocetoma.

In certain parts of India the feet of the natives are liable to a peculiar swelling; "tubercles" form beneath the skin, burst, and leave sinuses from which bodies, like those constituting the roe of a fish, are discharged, or, more rarely, bodies like grains of gunpowder. In the latter, fungous elements have been recognized, and were originally called *Chionyphe carteri*: they are now recognized as a form of Streptothrix (*Str. maduræ*). These are believed by some to be the cause of both classes of the disease. On section through a diseased part, masses of the above bodies are seen, especially in the fatty subcutaneous tissue; the masses may have no obvious communication with each other or with the surface. Kanthack considered the disease a form of actinomycosis: Boyce and Surveyor acknowledge the similarity, but not the identity, of the two, and this view at present prevails.

Streptothrix Infection.

Cases occur in which there is a generalized infection by a form of Streptothrix. In many instances the lungs have been the organs principally affected, the general characters of the lesions resembling those of tuberculosis; in others, abscesses have been met with in the brain and elsewhere. The branching mycelium of the fungus can be recognized microscopically after staining. The organism was first described by Eppinger: it grows readily on laboratory media and is pathogenic to rabbits and guinea-pigs.

CHAPTER XI.

DISEASES OF SPECIAL TISSUES AND ORGANS.

I. DISEASES OF THE CONNECTIVE TISSUES.

Inflammation of the Cornea.

SENFTLEBEN's experiments have shown that injury of the cornea produces none of the vascular signs of inflammation unless the marginal vessels are affected, or unless leucocytes are admitted from the conjunctival sac (p. 152). Anteriorly and posteriorly the cornea is limited by membranes sufficiently stout to resist the passage of leucocytes; but, in severe inflammation, leucocytes and fluid exudation from the vessels enter freely from the margin, passing along the lymph-channels in which the cells and nerves lie. The leucocytes thus accumulate in clusters around the corneal cells. Such exudation is accompanied by softening and opacity of the corneal structure, and may lead to alteration in its curvature. This happens in vascular *keratitis* and in the interstitial inflammation of congenital syphilis. When a slight proliferative inflammation occurs beneath the roughened epithelium as a consequence of the irritation of granular lids, the condition is known as *pannus*. Pus, forming between the layers of the cornea, constitutes *onyx;* and ulcers are common. Healing in all such cases is by scar-tissue, and some opacity and a more or less altered corneal curve (*anterior staphyloma*) are thereby produced. In the most intense forms of purulent conjunctivitis the injury to the cornea may be so great that it undergoes necrosis.

Inflammation of Cartilage.

In the most acute inflammations of joints the cartilage may slough, like the cornea, from injury and lack of nourishment. It then either peels off in flakes or softens and wears away at points of pressure. In less acute cases it may be invaded by leucocytes from the joint-cavity or from the bone (p. 380). Enlargement and multiplication of cartilage-cells may often be seen, as well as the accumulation of leucocytes (Fig. 230). In a joint with inflamed cartilages the effused fluid is always turbid from degenerating leucocytes and the resulting débris—thus differing from that of serous synovitis; and not infrequently the exudation becomes purulent. Healing takes place by the formation of scar-tissue from the new cells. Short, extremely strong and wide adhesions often bind the surfaces together, producing *fibrous ankylosis*: some of these bands may calcify. If the bone is laid bare some or all of the adhesions will ossify—*bony ankylosis*.

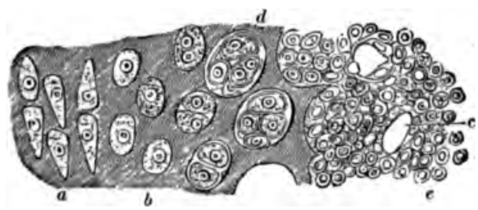
Chronic Rheumatoid Arthritis (Arthritis deformans).

It is probable that more than one condition is included under the term rheumatoid arthritis. One form which occurs in young persons and rapidly involves many joints, is not improbably an infective disease, due to some micro-organism; while the more common chronic form, whether one joint or many suffer, seems to be a degenerative or perhaps a "trophic" condition. The resemblance between the changes seen in osteo-arthritis and those of "Charcot's Joints" in tabes dorsalis, is very close. Some authorities maintain that these chronic cases are due to the action of micro-organisms of feeble virulence, or to toxines derived from local foci of infection (septic conditions of the mouth, tuberculosis).

The chronic form of the disease is characterized by degeneration and atrophy of certain of the articular cartilages, as well as by overgrowths from the margins of these cartilages, and from the synovial membrane.

The first change observed in the cartilage is fibrillation of the matrix,

FIG. 230.



Section of inflamed cartilage. *a*, the normal cartilage-cells; *b*, the same enlarged; *d*, multiplication of cells within their capsules; *c*, eroding layer of granulation-tissue, with (*c*) vessels. Some of the cells are probably invading leucocytes. × 250. (Cornil and Ranvier.)

followed by softening and erosion. The centre of the cartilage may be quite worn away and the bone beneath hardened and highly polished (*eburnation*). The outgrowths from the margins of the articular cartilages are subject to considerable variation in size. Sometimes they ossify and cause distinct limitation of the movements of the joint; sometimes they are so slight that no obvious deformity occurs. From the synovial membrane a large number of small fibrous nodules develop; some of them become calcified and present a rough worm-eaten appearance, and nearly all of them contain a small central cavity. The bands connecting these nodules to the membrane may occasionally become obliterated, and the small fibrous masses persist as loose bodies in the joint. These outgrowths are probably due to a *proliferative inflammation* of the normally existing villi of the synovial membrane.

The chronic changes which occur in joints, as the result of continued rheumatism, differ from the foregoing in so far as the cartilage becomes fibrous and not eroded, while no outgrowths occur from their margins and but little from the synovial fringes.

Gouty Arthritis.

In this disease acicular crystals of sodium biurate are deposited in both matrix and cells of the articular cartilages, each successive deposit being accompanied by an acute but evanescent inflammation of the joint. The cartilages become opaque, irregularly eroded, and here and there thickened (p. 75).

The deposits may take place so frequently and throughout so large an area, that cartilages, capsules, ligaments, bones, and surrounding tissues become completely infiltrated, giving rise to white mortar-like masses and considerable deformity. The distended and infiltrated skin over them is very liable to ulceration. The metatarso-phalangeal joint of the great toe is most frequently affected, but the other joints of the foot, and the small joints of the hand, are all very liable to the change.

No complete explanation of these changes can be given. The immediate cause has been supposed to be the conversion of sodium quadriurate, a fairly soluble salt, contained in the blood and lymph, into sodium biurate, a very insoluble salt, which is rapidly deposited. According to many authorities this is especially likely to occur when the amount of quadriurate in the blood becomes increased, owing to defective secretion by the kidneys. The very existence of quadriurates has, however, been called in question. Further, it is not certain whether the deposit of sodium biurate is the cause or the effect of inflammation occurring in the joint affected. (See Chapter XII.)

Inflammation of Periosteum.

Inflammation of bone always originates in its vascular structures—the periosteum and medulla. Although the term *periostitis* only implies that the *periosteum* is inflamed, the adjacent layers of the *bone* are always involved. When the inflammation chiefly affects the medulla and other soft parts lying in the Haversian canals or cancellous spaces, the condition is called *osteitis*; but when the medulla in the canal of a long bone is most markedly involved, the term *myelitis* is employed. Inflammation is never strictly limited to either of these parts; hence the term *osteomyelitis*.

Periostitis may be conveniently divided into three varieties: *serous*, *proliferative*, and *suppurative*.

1. **Serous periostitis** is rare, and is the mildest form of infective inflammation of the part. The exudation is highly albuminous.

2. **Proliferative periostitis** is common as a result of injury and of syphilis. A projecting node is formed of proliferated cells from the deeper layer of the periosteum, as well as of emigrated leucocytes. These cells may disappear, or may, as in other cases, be succeeded by fibrous tissue. This may ossify: it very rarely breaks down. Ossification begins in that part of the new tissue which is in contact with the surface of the bone. The vessels entering the Haversian canals in the

latter are, on account of the elevation of the periosteum, more or less vertical to the surface; hence the new Haversian canals have the same direction. These new canals are at first well defined and easily separable from the old, but both ultimately become blended. The periosteum of bones lying just beneath the skin is especially liable to proliferative inflammatory changes. Inflammatory enlargement of a bone is always due to periostitis.

3. **Suppurative periostitis** is generally a part of the infective disease known as *acute necrosis* or *osteomyelitis*. It affects growing bones, and rarely, if ever, occurs after union of the epiphyses. This disease is often associated with obvious injury: in other cases it is not improbably preceded by some minute lesion, such as a capillary hemorrhage or partial separation of an epiphysis. Pyogenic organisms lodge in the wide capillaries of the shaft, close to the epiphysial disc, and excite suppuration. This spreads outward along the disc and then beneath the periosteum. Sometimes the organisms may affect the periosteum primarily. In both cases pus, forming beneath the periosteum, rapidly separates it from the bone. The vessels passing inward from the periosteum are thus greatly stretched, and this, together with the primary damage to the vessels, induces thrombosis in many of them. Hence *superficial* necrosis is the usual result; but if the medulla also has suppurated, the necrosis will be *total*—*i. e.*, will involve the whole thickness of the shaft. Pyæmia may occur if the abscess is left unopened; and this is the condition in which infective fat-embolism is most likely to occur. In **septic osteomyelitis**, following operations in which the medullary cavity has been opened, a diffuse suppurative inflammation attacks the medulla and, to a less extent, the periosteum, causes total necrosis of large portions of bone, and very frequently produces a fatal result from pyæmia (p. 342).

Inflammation of Bone.

Osteitis is generally divided into two principal varieties: (1) *rarefying osteitis* or *caries*, and (2) *condensing osteitis* or *sclerosis*.

1. **Rarefying Osteitis (Caries).**—In the mildest form the occurrence of granulation-tissue is the first change observed. This occurs much oftener in cancellous (vertebræ, tarsus, carpus, epiphyses of long bones) than in compact bone. A round-celled infiltration takes place in the medulla and presses into the Haversian canals; the fat-cells and the hard substance of the bone disappear before it—cancellous trabeculæ are eaten through and Haversian canals widened. A section shows spaces crowded with cells, often developing here and there into fibrous tissue. On the surface of the bone, bordering these spaces, are seen semilunar erosions, as if small bites had been taken out of it. These are called Howship's lacunæ. Each contains leucocytes and epitheloid cells (osteoblasts), and often a giant-cell (osteoclast). The giant-cells erode the bone. The normal bone-corpuscles remain unchanged so long as they are distinguishable. This process may be described as an ulceration or *caries*

of bone without formation of pus (*caries sicca*). Bones thus weakened yield to pressure; thus the readily affected bodies of vertebræ may almost disappear, those above and below becoming approximated (*Pott's disease*); while the shafts of long bones bend, as is seen in *osteitis deformans* and other diffuse inflammations. The inflammatory tissue may pursue any of the courses mentioned on p. 173 *et seq.*

In a very early case absorption of the inflammatory exudation may occur, and regeneration make good any loss of bony tissue which has taken place; but when marked destruction of bone has occurred, healing can only be effected by the formation and ossification of scar-tissue. This occurs in cases of healed spinal curvature without abscess. Too often, however, the cells degenerate, and a *cold abscess* results (p. 175). When this is open, the ulcerating, *carious* surface of bone is exposed. If healing occur, it is by the process just described. Caries resulting in *cold abscess* is generally a manifestation of tuberculosis. It is sometimes due to syphilis.

If the infiltrating granulation-tissue degenerate (p. 379), death of the infiltrated bone ensues: the pieces which come away are generally of small size—*caries necrotica*.

2. Condensing Osteitis (Sclerosis).—In the most chronic forms of osteitis no rarefaction of bone occurs; the new growth slowly ossifies and the Haversian canals and cancellous spaces diminish. The bone consequently becomes extremely heavy and ivory-like; it is generally thickened irregularly from coincident periostitis. Syphilis is the commonest cause of this change, especially in the long bones and in the bones of the skull. It is said that simple closure of a large number of Haversian canals may lead to death of the affected bone. In syphilitic necrosis of the skull the sequestrum is often very dense; it has probably been killed by degeneration and death of the inflammatory products in the bone around the sclerosed patch, with the consequent destruction of the few vessels which entered it.

It is common to find rarefying and condensing osteitis combined. Osteoplastic periostitis and condensing osteitis frequently exist around carious patches; the surrounding bone is thus rendered thicker and denser. It may be that this less acute inflammatory process is coupled with true hyperplasia of the bony tissue.

Necrosis of Bone.

It has already been shown that death of bone may follow, in several ways, different forms of inflammation, each leading, however, to destruction of vessels and arrest of nutrition.

This result may be brought about by any *injury* which strips off the periosteum and breaks up the medulla; but the extreme rarity of necrosis, even in the most serious simple fracture, shows that injury alone, with such inflammation as it excites, is scarcely to be regarded as a sufficient cause. It may, however, act indirectly by preparing a nidus for pyogenic and other infective organisms, as in compound

fractures. Such intense irritants so diminish the vitality that more or less extensive thrombosis occurs, with death of the parts which they supply.

Suppuration, beneath the periosteum and in the medulla, is the commonest cause of necrosis. This result is more often produced in compact than in cancellous tissue, owing to the greater ease with which the exudation can compress the vessels in the smaller and less numerous channels of the harder tissue.

The piece of dead bone is called a *sequestrum*: it is cast off by a process of caries which destroys the attachments of the sequestrum to the living bone beyond. It may be total—involving the whole thickness—*superficial*, or *central*—the last being much the rarest.

Considerable difficulty is often experienced in the removal of the sequestrum, especially if it be deeply seated. This difficulty is occasionally (*in central necrosis*) due to the persistence of a layer of the old bone enclosing the necrosed portion. Much more frequently, however, it is owing to the participation of the periosteum in the inflammatory process. The inflamed periosteum produces new bone, and the bony capsule (*involucrum*) thus formed encloses the sequestrum. Openings (*cloacæ*) exist in this capsule leading to the dead bone, and through these openings the inflammatory products are discharged. When the sequestrum is quite superficial its removal is, of course, more readily effected.

Mollities Ossium.

Mollities ossium, or Osteomalacia, is a rare disease, occurring only in adults, and especially in pregnant women who have borne many children. It is characterized by progressive decalcification of the bones, whilst the marrow increases steadily and becomes converted into a vascular round-celled structure. All bone is gradually absorbed, except a thin layer beneath the periosteum; so that in extreme cases the bones become mere shells. They are very light, easily cut with a knife, and bend or break readily. Early in the disease fractures may still unite. On section, in early stages, the cancellous spaces and Haversian canals are enlarged and full of a reddish, gelatinous substance, which at a later period may become yellow and fatty.

The nature of the disease is obscure. Lactic acid has been found in the bone—the reaction of which is said to be acid—and in the urine. The latter usually contains excess of calcium salts which have been removed from the bone and excreted.

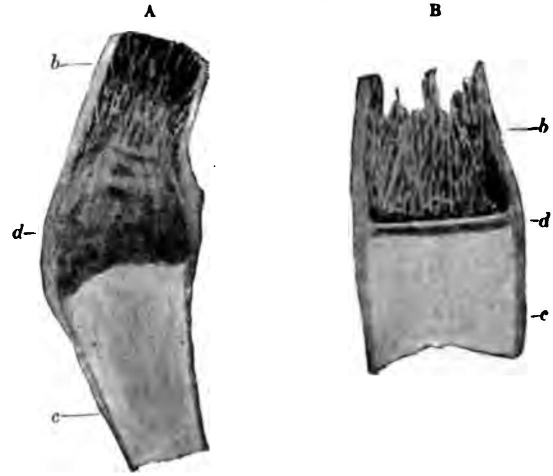
The pelvic deformity resulting from the disease is clinically the feature of chief importance: the sacrum is pushed downward by the weight of the body, and the acetabula upward and inward by the resistance of the femora, thus greatly shortening the two oblique diameters (p. 410).

Rickets.

This disease of children is so frequent in the towns of England that it has acquired on the continent the name of the "English disease." It appears to be caused by defective hygienic conditions, especially by bad air and improper feeding. It is particularly common in children brought up by hand, especially in infants which receive starchy food at an age when they cannot properly digest it. It may probably be said that all conditions which materially interfere with the nutrition of a child aid in the causation of rickets; among these, the absence of *fresh* food ranks high. Diets deficient in fats or in carbohydrates seem sometimes to be sufficient causes.

The disease is mainly characterized by changes affecting the growing parts of bones, and is therefore most marked where growth is most active—viz., at the epiphyses and under the periosteum of long bones, and at the margins of flat bones. These changes produce undue thickness and softness, which, in their turn, lead to projections and curves, according to the direction and degree of the pressure on the softened bones. The bone-lesions are accompanied by symptoms of general ill-health, and often by enlargement of the liver, spleen, and,

FIG. 231.



Growing ends of (A) rickety and (B) normal ribs. B is taken from an older child and is therefore larger (see text). *b*, rib; *c*, costal cartilage; *d*, transition zone. × 3.

less often, of the kidneys and lymphatic glands, due chiefly to increase of their interstitial connective tissue.

The essential changes in the bones are (1) an excessive absorption of pre-existing bony tissue, and (2) an extensive formation of osteoid tissue (p. 112), which very gradually and very imperfectly undergoes calcification. It will be remembered that if a section of the end of a *healthy* growing long bone be examined, a straight line is seen where the white epiphysial cartilage is adherent to the shaft (Fig. 231), which

here consists of loose cancellous tissue, with spaces filled with red marrow. Between the bone and the epiphysis is a blue semi-translucent band about one millimetre broad with practically straight margins. Microscopically, the blue line is found to consist of the one or two layers of cartilage-cells which normally multiply and enlarge, forming the well-known oval groups among which ossification proceeds. The septa between these groups become very thin and, in the immediate neighborhood of the shaft, undergo calcification. A sudden transition from the cartilage-cells to those of the vascular red marrow is seen in these spaces. As soon as these spaces (*primary areolæ*) with calcified walls become occupied by the round-celled marrow, absorption begins, and adjacent spaces open into each other and form the larger *secondary areolæ*. On the walls of these, laminæ of bone are deposited, including osteoblasts in the lacunæ between them; and thus Haversian systems are gradually developed. The calcified cartilage-matrix is darker and more granular than the bone laid down by the medulla which gradually replaces it.

In a rickety bone the blue transition-zone is at least ten times wider than normal, affecting many rows of cartilage-cells; while its outlines, both toward the bone and toward the cartilage, are very irregular (Fig. 231). The calcification of the matrix occurs without any regularity. In the cartilage, among the long rows of proliferated cells, will be found spaces which arise as outgrowths from the medulla and contain vessels and medullary tissue. Just reaching and partly surrounding these are thick irregular trabeculæ of osteoid tissue, which enclose masses of cartilage, here and there calcified, and of medulla. The trabeculæ are thickest and most extensive on the medullary side of the proliferating cartilage-cells. In the central parts of some of the thickest trabeculæ small patches of true bone may be seen. A few of the cartilage-cells may become converted into marrow cells, as in normal ossification; but a large number are converted directly, without any rupture of their capsules, into the cells of the osteoid tissue (Fig. 232).

In flat bones the process begins by a very marked absorption of the already formed bony trabeculæ. Upon the remnants of the old bone, as well as in the spaces between them, osteoid tissue is deposited so as to form new trabeculæ in the marrow. The formation of the osteoid tissue is preceded by a spindle-celled embryonic tissue. Beneath the periosteum osteoblasts form and osteogenic fibres appear. From these, osteoid tissue is formed. In general terms the growth of osteoid tissue in the medulla may be said to resemble the formation of internal callus, while that deposited from the periosteum similarly resembles external callus (Ziegler).

Bones consisting of soft rickety structure yield more or less readily under pressure, or break under slight violence. The fracture, however, is generally incomplete. As bending occurs, a buttress of bone is deposited along the concave side of the curve. This is often seen in the femur and tibia, giving the bones a flat, somewhat razor-like appearance. The position and extent of the curving will depend to some extent upon

the relative proportion which the changes at the epiphyses bear to those beneath the periosteum.

These changes afford a ready explanation of (1) the thickening of epiphyses, (2) the displacements which occur about the junction of shafts with epiphyses, (3) the thickenings of the edges, and the irregularities on the surface, of cranial bones, and (4) the abnormal curvature of bones under pressure—all of which are common phenomena in rickets.

The process just described seems to be injurious to the subsequent growth of the epiphyses. They often join the shafts prematurely, and thus cause permanent shortening of the bones.

Among the most important of the deformities resulting from this disease is the **rickety pelvis**. There are two forms. The first shows *shortening of the antero-posterior diameter* only, and occurs in cases in which the child, being unable to walk, is kept lying down. The second resembles the *osteomalacic pelvis*, both in its shape and in the mechanism of its production, for it occurs in children who are able to walk about (p. 408). In a **rickety thorax**, the growing anterior ends of the ribs are softened and much enlarged, especially on the visceral side. *The softening* leads to a sinking in of the softened parts and to a corresponding pushing forward of the sternum ; while *the enlargements* produce a row of nodules on each side of the thorax, diverging from above downward (*rickety rosary*).

Along with the changes in the bones just described the principal features of rickets are : delayed dentition, early decay of the milk-teeth, late closure of the fontanelle, laxity of the ligaments surrounding the joints, a tendency to catarrh of mucous membranes, and an undue irritability of the nervous system ; to this last condition are due the convulsions which occur in rickety children on slight provocation, and the special forms of spasm known as tetany and laryngismus stridulus.

II. DISEASES OF LYMPHATIC GLANDS.

Inflammation.

Examples of **acute inflammation** of lymphatic glands (*acute lymphadenitis*) are furnished by the inflammation of the axillary glands which may follow a wound on the hand ; of the inguinal glands, in a case of soft chancre ; and of the lymphoid follicles of the intestine in inflammation of the intestinal mucous membrane.

In acute inflammation of lymphatic glands the bacteria which produce the inflammatory reaction, or their toxines, are generally conveyed from a primary focus of inflammation (diphtheritic, erysipelatous, scarlatinal, chancrous, etc.), existing in the area of skin or other tissue drained by the lymphatics leading to the gland : occasionally no seat of infection is apparent, and the bacteria seem to have been conveyed directly to the gland without causing any lesion elsewhere. A gland affected by acute inflammation becomes intensely vascular, and the seat of free exudation. The escaping leucocytes accumulate in its tissues and sinuses, until all distinction between medulla and cortex has

FIG. 232.

ing end of rickety rib. *a*, cartilage; *b*, *b'*, *b''*, vascular medullary spaces within cartilage; *d*, proliferating cartilage-cells; *e*, calcified cartilage; *f*, vascular channels; *g*, trabeculæ osteoid tissue; *h*, vascular medulla; *i*, true ossification occurring in osteoid trabeculæ.

disappeared, while the gland is swollen and its substance is soft, pulpy, and often dotted with hemorrhages. Leucocytes in the lymph coming from the primary focus are also detained in the gland.

Upon the removal of the injurious influence, the process may gradually subside, and the new elements undergo disintegration and absorption, the gland gradually returning to its normal condition (*resolution*).

In other cases the process may be more intense and go on to *suppuration*. Scattered areas may necrose, trabeculæ be destroyed, many of the cells become disintegrated, and the loculi of the gland become filled with pus. This is usually associated with inflammation and suppuration of the surrounding connective tissue. In the glands of a mucous membrane the process gives rise to what is known as a *follicular abscess* (p. 415). In still more acute cases the exudation may be largely hemorrhagic.

Chronic inflammation of lymphatic glands results from the presence of irritants which, while less severe, are more prolonged in their action than those which give rise to the acute form. The commonest infective causes are tuberculosis and syphilis, and the commonest non-infective cause is the presence of dust, and especially particles of carbon. The lymphadenitis due to tuberculosis or syphilis is marked by increase in the number of cells, followed by fatty degeneration and caseation. The gland may be enlarged to many times its natural size. In some cases the reticulated network becomes thicker and more fibrous, its meshes becoming smaller and smaller; the lymph-cells diminish in number; and the gland becomes hard and fibrous (Fig. 223). Probably in these chronic cases the cells of the gland-substance and the flat connective-tissue cells covering the trabeculæ multiply, and assist in forming the new cells. Fatty patches are frequent in such glands. In lymphadenitis due to the presence of dust the thickening of the reticular network is the principal change. This may also form the final stage of *acute* lymphadenitis.

FIG. 233.

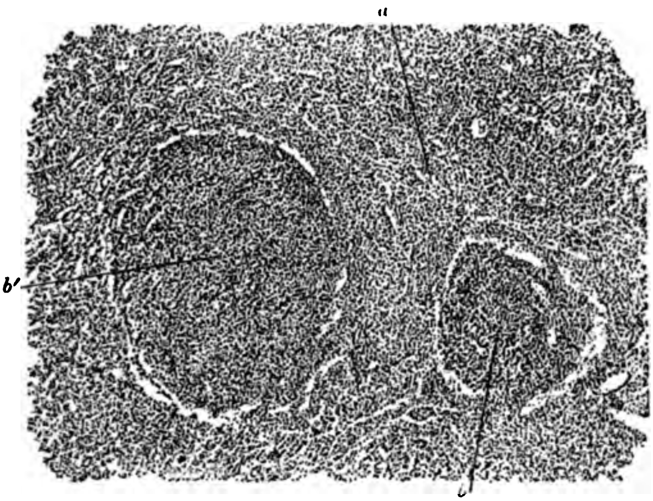
Chronic inflammation of a lymphatic gland. Showing the increase in the stroma, and the diminution in the number of the lymphoid cells. × 200.

Post-nasal "Adenoids."

Masses of adenoid growth not infrequently develop from the roof and posterior surface of the naso-pharynx in weakly children. These masses consist of ordinary soft lymphoid tissue with the cells here and

there more closely aggregated into follicles (Fig. 234). The growths are covered by ciliated epithelium, but this is often destroyed by the catarrhal processes to which they are liable. They interfere with the passage of air through the nose, and often block the orifices of the Eustachian tubes. In a few instances they show tubercular changes.

FIG. 234.



Section through a post-nasal adenoid growth. *a*, soft lymphoid tissue with extremely little stroma; *b*, *b'*, lymphoid follicles, cells more closely aggregated. × 70.

Hodgkin's Disease (Lymphadenoma).

This disease is characterized by the enlargement of the lymphatic glands and lymphoid tissue in various parts of the body, together with the development of lymphatic growths in internal organs, especially in the spleen, and by a progressive diminution in the number of the red corpuscles in the blood.

The larger lymphatic glands are usually the earliest seats of the growth. At first only a single group of glands may be enlarged; subsequently, however, the process becomes more general, and the glands throughout the whole body may be more or less involved. The groups of glands most often affected are, in the order of frequency, the cervical, axillary, the inguinal, the retro-peritoneal, the bronchial, the mediastinal, and the mesenteric. The growth, which in the earlier stages is limited to the glands, gradually breaks through the capsules, so that the enlarged glands ultimately become confluent, and form large lobulated masses; but the agglomeration of glands in Hodgkin's disease is generally a later and less prominent feature than in tuberculosis of lymphatic glands. The growth may also extend still further beyond the confines of the gland, and invade and infiltrate the adjacent structures.

This new growth of lymphatic tissue, which commences in and often extends beyond the confines of the lymphatic glands, is ultimately followed by the formation of lymphoid growths in various internal organs wherever lymphoid tissue exists, but more especially in the spleen, which is affected in a large proportion of cases. Here the new growth originates in the Malpighian bodies, and so gives rise to disseminated nodules. These vary in size from minute points to masses as large as a hazel nut or walnut. They are usually more or less irregular in shape, of a grayish or yellowish-white color, firmer in consistence than the splenic tissue, and not encapsuled. In addition to these, wedge-shaped infarctions surrounded by a zone of hyperæmia are sometimes met with, similar to those which are often seen in leucocythæmia. The spleen itself is generally somewhat increased in size, and its capsule is usually thickened, and often adherent to adjacent organs. In quite exceptional cases the spleen is not the seat of these disseminated growths, but is simply enlarged, like the leucocythæmic spleen.

The liver, kidneys, alimentary canal, medulla of bone, lungs, and subcutaneous tissue may all become involved, the new growths occurring either as nodules of various sizes scattered through the organs, or in a more infiltrating form, like many of those met with in leucocythæmia.

In their structure these growths present at first no striking differences from ordinary lymphatic glands. The various parts of these are clearly recognizable, though the number of lymphocytes in the reticulum is much increased. Later on, the septa appear split up, while the interstices thus formed are filled with leucocytes, among which there appear epithelioid (endothelial) cells and giant-cells: these are scattered about irregularly and are not arranged in "systems," as in tuberculosis. The giant cells may contain one or more nuclei. In old cases the glands may be entirely fibrous. The lymphoid masses present differences in the relative proportions of cells and stroma. The richly cellular forms are soft and pulpy, whilst those in which the stroma is more abundant are firmer and more fibrous in consistence (Fig. 233). Retrogressive changes are infrequent. There is rarely any notable increase in the number of leucocytes in the blood, but the red corpuscles are diminished in number (anæmia). It is said that new lymph-glands are formed in this disease to compensate the destruction of the original glands. These new glands subsequently suffer from the pathological process at work.

The pathology of the disease is undoubtedly obscure. The development of the new-growths cannot in most cases be regarded as the result of infection, though one instance is recorded in which an assistant, shortly after being concerned in the clinical investigation of a case, developed the disease in a very acute form. The disease occurs in many of the lower animals. A bacillus has been credited with the production of the disease, but further evidence is necessary before this theory of causation can be accepted.

III. DISEASES OF MUCOUS MEMBRANES.

There is sufficient similarity between the diseases of the various mucous membranes to justify a general consideration of their characters.

Inflammation.

It is convenient to distinguish certain varieties of inflammation of mucous membranes according to the degree of damage to the tissues, the depth to which it extends, and the general character of the exudation. In each of these varieties the usual changes in the blood-stream and vessel-walls occur, leucocytes and fluid escaping into the tissues and on to the surface of the membrane. The two main varieties into which inflammation of mucous membranes may thus be divided are (1) *catarrhal*, in which the exudation remains fluid; and (2) *fibrinous*, in which it coagulates, forming the so-called *false membrane* on the surface.

Catarrhal Inflammation.—In this form the exudation may be serous, mucous, mucopurulent, or purulent, according to the nature and intensity of the irritant.

Serous Catarrh.—In acute cases the earliest signs of simple inflammation (p. 180) are rapidly followed by a copious watery exudation from the surface, and the tenderness and pain are soon relieved. When the onset is less acute, the early changes are less marked, the exudation being usually the first thing noted. These changes are frequently met with in ordinary nasal catarrh.

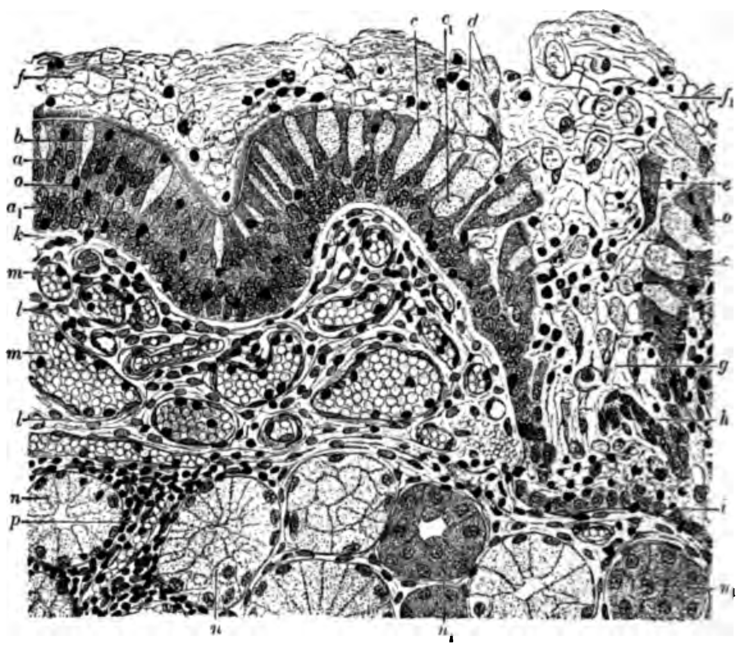
Mucous Catarrh is characterized by increased production of mucus derived from the surface-epithelium or secreted by the mucous glands (Fig. 235). The mucus escapes with the serous exudation, or remains more or less adherent to the surface, as is often seen in chronic pharyngitis. Sometimes the seromucous discharge is practically clear; at others, it is more or less opaque: in the former case, it contains only a few cells: in the latter, a large number. The cells are either escaped leucocytes or desquamated epithelial elements, detached, for the most part singly.

Purulent Catarrh.—If the irritation be more intense and give rise to a chemotactic substance, the number of leucocytes escaping will be still greater, and the secretion will be purulent or mucopurulent. In such cases the epithelium is often detached in considerable masses, and the underlying tissue markedly infiltrated with leucocytes. The basement-membrane is œdematous and the whole mucosa swollen. All *lymphoid structures* in the mucous membrane are generally affected. The lymph-follicles swell, their contents soften, and minute abscesses are formed; the latter burst and leave the small ulcers (*follicular ulcers*) so often seen in severe catarrh of the intestines, appendix vermiformis, and pharynx. The ulceration in some cases extends beyond the confines of the follicle. Not infrequently the proper *glandular*

structures also become involved, and their ducts may become choked with the products of their altered secretion.

The acute process may quickly subside, or it may become chronic. In the former case the damaged epithelium is soon replaced, the repair often beginning before the vascular changes have disappeared. In the latter case (*chronic catarrh*) the hyperæmia diminishes, but the escape of leucocytes and the multiplication and desquamation of epithelial cells continue, while the sub-epithelial tissue remains extensively infil-

FIG. 235.



Recent catarrhal bronchitis. *a*, ciliated cells; a_1, deep layers of cells; *b*, goblet-cells; *c*, cells that have undergone extreme mucoid change; c_1, mucoid cells whose nuclei have undergone a similar change; *d*, desquamated mucoid cells; *e*, desquamated ciliated cells; *f*, deposit consisting of mucus-droplets, and, f_1, of mucus-filaments and pus-corpuscles; *g*, excretory duct of a mucous gland filled with mucus and cells; *h*, desquamated epithelium of the excretory duct; *i*, persistent epithelium of the duct; *k*, swollen hyaline basement-membrane; *l*, connective tissue of the mucosa somewhat infiltrated with cells; *m*, distended bloodvessels; *n*, mucous glands filled with mucus; n_1, acini of mucous gland without mucus; *o*, migratory cells in the epithelium; *p*, cellular infiltration of the connective tissue of the mucous glands. 120. (Ziegler.)

trated with leucocytes. Later on, the epithelium and the glands may undergo atrophy, while the sub-epithelial connective tissue may become more and more extensively infiltrated with small cells, due to multiplication of connective-tissue cells, leading ultimately to marked fibrosis. When stretching of the mucous membrane accompanies atrophy of the glands, as in chronic catarrh and dilatation of the stomach, the membrane is often much thinner than normal.

The changes in the subepithelial connective tissue are usually accompanied by enlargement of the lymphoid structures—an enlargement which sometimes gives to the membrane a nodular or granular appearance. This is well seen in the pharynx (*follicular pharyngitis*). The enlarged lymphoid structures may ulcerate, and the muscular and elastic tissues, although they lie some distance from the surface, may be so far weakened that when considerable pressure is put upon them—as by the cough of chronic bronchitis—they may give way, and permit dilatation of the tubes they surround. The muscularis mucosæ when damaged is never completely repaired. After death any hyperæmia present rapidly disappears, and is seldom recognizable even in severe cases: the mucous membrane may even look paler than natural; but, after repeated inflammation of any intensity, more or less dark-gray pigmentation from extravasated blood will, in most situations, bear evidence of the former attacks. These appearances can readily be seen in a chronically inflamed bladder such as is associated with stricture of the urethra, or enlarged prostate.

Ætiology.—The causes of catarrhal inflammation are (1) the entrance of mechanical or chemical irritants into the cavities or tubes lined by mucous membranes; and (2) the presence and growth of bacteria and other parasites.

As examples of the first of these causes may be quoted the production (1) of bronchitis by metallic particles or irritating vapors in the respired air; (2) of gastric catarrh by the action of alcohol; and (3) intestinal catarrh by the passage of irritating ingesta. As examples of the second group may be quoted the catarrh of the large intestine due to the presence of thread-worms, and the urethral catarrh caused by the introduction and growth of gonococci.

The two causes above mentioned may frequently be combined. They are probably assisted to some extent by exposure to cold, as in intestinal catarrh, and by certain abnormalities in the circulatory blood such as are believed to exist in gout.

Fibrinous Inflammation.—This term is applied to those inflammations of mucous membranes and open wounds which are characterized by the production of a fibrinous layer or so-called *false membrane*—such as is seen in diphtheria. On mucous surfaces the exudation may exist in little patches or may cover a large area. It is usually of a yellowish or grayish-white color, and its consistency varies from a firm and tough membrane to a soft, pultaceous material; it may be deeply blood-stained. It is more or less easily separable from the subjacent tissue, and when removed carries at least the surface-epithelium with it. In thickness it may vary considerably in different parts. The words *croupous* and *diphtheritic* are often applied to conditions of fibrinous inflammation, and are sometimes used to distinguish different degrees of the process. Thus some authorities call an inflammation *croupous* when the membrane involves no more than the *epithelium* of a mucous membrane, and *diphtheritic* when it involves the whole *mucosa*. This difference in the depth of the tissues involved is probably due to

variation in the intensity of the irritant, the extent of the *false membrane* in diphtheritic inflammation being due to the coagulation-necrosis (p. 36) of the involved mucous membrane. The use of the term *diphtheritic* in this connection is unfortunate as it does not imply any necessary connection with *diphtheria*, although this disease undoubtedly furnishes the best examples of diphtheritic inflammation. It is better, therefore, to discard these unnecessary terms, and to speak of fibrinous inflammation, recognizing that this may vary in intensity, and consequently in the degree of destruction of tissue that it induces. According to Cohnheim, the process is more likely to be superficial in those situations where a distinct basement-membrane exists—as in the pharynx and respiratory tract—than in those where this is not the case—as in the intestines and conjunctiva.

False membranes differ in character according to the depth of tissue involved. If only the epithelium be destroyed, the membrane is thin and easily stripped off. It consists of several layers of fibrin containing in their meshes leucocytes, desquamated epithelial cells and débris; and lies on the surface of the hyperæmic mucous membrane, which is denuded of its epithelium and infiltrated with leucocytes. If the whole mucosa is involved, as in diphtheria, the false membrane is separated with difficulty, and its deeper parts are found to contain necrosed tissue. In such cases a bleeding surface is left when the membrane is removed. In advancing cases there is no sharp line between the coagulated and the living tissue-elements.

Etiology.—The apparent causes are very varied. False membranes are found (1) on the tonsils, larynx, and other parts in affections due to the B. diphtheriæ and to other organisms (streptococci, pneumobacilli), or as a result of scalds or the application of caustic chemicals; (2) in the bladder after parturition (when a complete cast may be expelled), and in the most acute cystitis; (3) in the vermiform appendix, sometimes from the irritation of a concretion; (4) in the lower part of the large intestine in dysentery; and (5) as a chronic change in the air-tubes in plastic bronchitis. It may be noted here that false membranes sometimes form upon granulating wounds, and it is held by some that there is no real distinction between such cases and those of true diphtheria of wounds and of hospital gangrene. It seems most probable, however, that there is an etiological difference, for false membrane on granulations may be induced by merely blistering the surface.

Although the above facts show that false membranes may result from the action of simple irritants, the great majority met with in man are due to the action of pathogenic organisms, for most of them are contagious and organisms are found in almost all cases.

Effects.—The effects of inflammation of mucous membranes, whether catarrhal or fibrinous, depend very largely upon the size and function of the tubes or cavities involved. Acute catarrh generally gives rise to pain and to spasm of the involuntary muscular tissue, as is seen in the intestinal catarrh of children. When the tubes affected are small, obstruction to the passage of the secretions which they convey may

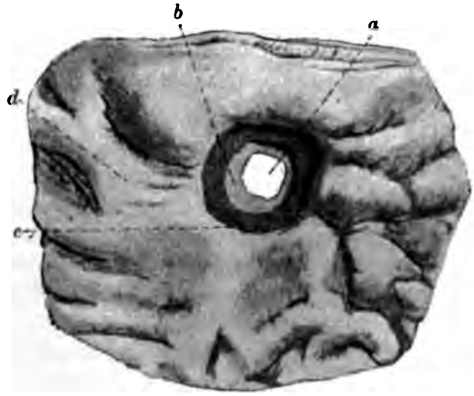
lead to serious results. Thus catarrh of the small bronchial tubes or diphtheritic inflammation in the larynx and trachea may so obstruct the entrance of air that the oxygenation of the blood is gravely interfered with, while catarrh of the bile-ducts may similarly prevent the bile reaching the intestine and lead to jaundice (p. 81). When much inflammatory fibrosis has occurred, marked irregularity or narrowing (*stricture*) of the lumen of the affected tube may result. The best illustration of this termination is seen in the result of repeated attacks of gonorrhœa. In this disease the purulent catarrh of the urethra is often followed by so much proliferative inflammation of the submucous tissue that the lumen of the tube is almost occluded. In structures of less importance, if the occlusion is complete, retention-cysts may be formed by distention behind the stricture (p. 158). When the obstruction is permanent but not entire, hypertrophy of the muscular walls above the stricture is usually found (p. 86).

Gastric Ulcer.

It occasionally happens that the nutrition of some small area of the wall of the stomach is interfered with, either by some local disturbance in its blood-supply or by some injury to its mucous surface. When this occurs the gastric juice, especially if its acidity be increased, acts upon the damaged or necrosed area and rapidly produces an ulcer. Such lesions may be found both in the stomach and in the upper part of the duodenum, but are commonest near the pyloric end of the lesser curvature of the former organ.

When seen in their most acute stage these ulcers are generally less than an inch in diameter. The inflammatory changes in the walls of

FIG. 236.



Acute perforating gastric ulcer. *a*, perforation in peritoneum; *b*, peritoneum; *c*, muscular coat of stomach; *d*, mucous membrane.

the ulcer are so slight that the latter are not appreciably thickened. The ulcer varies in depth: in some cases it only reaches the sub-

mucous tissue; in others it may penetrate the muscular and even the peritoneal coat as well. In the latter case the aperture in each coat is smaller than that in the coat immediately above it, so that the hole or ulcer has a funnel-shaped or shelved appearance when seen from the interior of the organ (Fig. 236). When the process of formation is more gradual, this shelved appearance is lost and some slight thickening of the walls is visible. Any organ adjacent to the ulcerated part of the stomach—*e. g.*, pancreas or liver—may become adherent and the ulceration may extend into its substance, so that it may form the floor of the ulcer. The longer the ulcer has existed the less typical are its appearances; when some weeks or months have elapsed, its outline becomes irregular, its walls thickened, its floor roughened, and its extent often considerably increased.

Healing may occur by regenerative proliferation of the adjacent undamaged tissues. In this process even the glands may to some extent be reproduced; but some puckering always remains as a result of the inflammatory repair, and the muscular layers are rarely, if ever, regenerated. In the course of such an ulcer, especially of the acute variety, two accidents are very liable to occur. The first of these is severe *hemorrhage*. When it is remembered that the principal vessels supplying the walls of the stomach lie in the submucous tissue, it is easy to understand how readily one of these main trunks may be laid open by the necrotic process just described. The second accident is *perforation* of the wall of the stomach. In the case of deep and acute ulceration the peritoneal coat is not infrequently perforated before the wall of the stomach has become firmly adherent to any other organ. Copious or repeated hemorrhage may give rise to fatal anæmia and syncope: perforation is almost invariably followed by acute suppurative peritonitis. Cicatrization of a chronic ulcer may be accompanied by so great a contraction of the resulting scar that either obstruction of the pylorus may occur, if the ulcer is situated near to this opening, or the stomach may be much deformed (hour-glass contraction) if the scar be situated toward the central part of its wall.

The mode of causation of gastric ulcers has been much debated. It has been suggested that embolism or thrombosis of a small artery may occur, and that death of a portion of the mucous membrane may result; but of this occurrence there is no sufficient evidence. Ulcers have been produced experimentally in dogs by feeding them with very hot food, but this mode of causation is unlikely to occur in mankind. Bolton produced ulcers in guinea-pigs by injecting them with a cytolytic serum produced by injecting rabbits with macerated gastric mucous membrane derived from other guinea-pigs, but this again throws little light on the human disease. The association of gastric ulcers with chlorosis and with hyperacidity of the gastric juice seems well established. Micro-organisms have been found in the tissues round the ulcers, but their presence is probably the result of secondary infection after the lesion has occurred.

In the *duodenum* ulcers may be met with after severe burns of the skin: they appear to be due to necrosis of the glands of Brunner.

Ulceration of the Small Intestine.

In the small intestine the forms of inflammation which require special consideration are principally those in which the lymphoid tissue is mainly involved. Some inflammatory swelling of Peyer's patches and of the solitary glands occurs in *diphtheria* and in *scarlet fever*, but in neither of these diseases does the lymphoid tissue often undergo necrosis, and only rarely, therefore, does ulceration occur. On the other hand, in *tubercular* infection of the intestine, ulceration is usual; and in *typhoid fever*, almost invariable. Tubercular infection has already been considered (p. 376); the lesions occurring in typhoid fever will now be described.

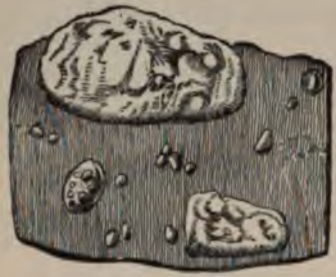
Typhoid fever is an acute infective disease, due to the action of the *Bacillus typhosus* (p. 317).

The ordinary duration of the fever is three or four weeks, and the temperature, as a rule, both rises and falls gradually. The most characteristic lesions are found in the solitary and agminated follicles of the intestine, the corresponding lymphatic glands, in the spleen, and sometimes the red marrow. The *intestinal* lesions are the most constant, and their various stages correspond so closely with definite clinical conditions that we can usually judge of the state of the intestine from the symptoms and the day of the disease. It is generally believed that infection occurs from the intestine, and that the intestinal lesions are points of inoculation. Thence the organisms spread to the mesenteric glands, spleen, liver, and kidneys, and are occasionally found in the urine. It is possible, however, that the disease is rather a general infection (septicæmia), the toxins of the bacilli especially affecting the lymphoid tissue.

The pathology and morbid anatomy of typhoid fever include other conditions due (1) to the direct action of the bacterial toxines and (2) to the depressing effects exerted by them upon the vitality of the tissues generally, which are therefore more than usually liable to invasion by other bacteria, such as pyogenic cocci and pneumococci. Thus, evidence of general poisoning is seen in the continued fever, which may assume a septic type, and even be accompanied by the formation of abscesses, probably resulting from a mixed infection. Cloudy swelling is found in many organs (p. 45), and the muscles are also especially liable to undergo the changes known as Zenker's degeneration (p. 65). Endocarditis is rare. Ulceration of the larynx, especially about the epiglottis, is occasionally present, and may lead to œdema of the glottis or to necrosis of the cartilages. Bronchitis is usual, and broncho-pneumonia may supervene; œdema of the lungs is common in fatal cases; and lobar pneumonia is a rather frequent complication in some epidemics.

The Intestine.—The most characteristic changes in typhoid fever take place in the solitary glands and Peyer's patches. In most cases the process is limited to those in the ileum and cæcum; and those glands are always most affected which are situated nearest to the ileo-cæcal valve. The cæcum is involved in one-third of the cases; ulcers may be present even in the rectum, but in the great majority of cases they are not found *below* the ascending colon. It is, moreover, unusual to find ulcers higher than nine feet *above* the valve, but they *may* extend into the upper part of the duodenum, or even be found in the stomach. The appendix vermiformis may also be affected.

FIG. 237.



Swelling of Peyer's patches and solitary glands of the intestine, as seen in typhoid fever.

The first change observed is a hyperæmia and **cell-infiltration** of the glands. Many of the cells increase considerably in size, and multinucleated forms are especially common. Both Peyer's patches and the solitary glands thus become considerably enlarged and prominent, and stand up, as sharply circumscribed, evenly raised areas, above the surface of the intestine (Fig. 237). Sometimes they slightly overlap the adjoining mucous membrane, and are surrounded by a hyperæmic zone. They are of a grayish-white or pale-red color, and of a soft brain-like consistence—the larger the size, the paler the color. The surrounding mucous membrane is also hyperæmic, and is the seat of an acute general catarrh, which is most pronounced before the glands swell. The cellular infiltration, in many parts, rapidly extends beyond the confines of the glands into the immediately surrounding and subjacent tissues, and in some cases even into the muscular and serous coats. Bacilli can be readily found during this stage, which ends in the first half of the second week of the disease.

The process now passes into the second stage—that of the death and disintegration of the newly formed tissue. Many of the enlarged glands subside, the new elements become fatty and are absorbed, and the inflammation thus undergoes a gradual process of **resolution.** But in other glands the intensity of the bacterial poison (p. 319) causes death of the inflamed lymphoid tissue. The necrosed tissues then separate. If a few scattered follicles in each patch have alone been destroyed, only small sloughs will be formed; and after the separation of these, the Peyer's patches thus affected will assume a peculiar reticulated appearance. If, on the other hand, as is most usual, the entire lymphoid mass is killed, this will separate as one or

FIG. 238.

A typhoid ulcer in which slough has entirely separated.

more large sloughs (Fig. 239), and the typical **ulceration** will be produced. Resolution or necrosis *begins* during the latter half of the second week. In the case of necrosis, the sloughs *separate* toward the end of the third, or during the beginning of the fourth week. This is the period of danger in which either severe hemorrhage or perforation into the peritoneal cavity may take place.

FIG. 239.

A Peyer's patch from a case of typhoid fever, in which death occurred at the beginning of the fourth week. *a*, a small ulcer from which the slough has separated, leaving a clean floor (muscular layer) and undermined edges; *b*, centre of Peyer's patch, from which slough is in process of separation as a single mass, being only adherent at *c*.

Although, as already stated, the cell-infiltration may extend beyond the confines of the glands, this is rarely the case with the ulceration. The peripheral infiltration undergoes resolution, and hence the ulcers have the same configuration as the original glands—those originating from the patches being oval, with their long diameters in the direction of the gut; and those originating in the solitary glands being circular in shape, like those arising from partial sloughing of a patch. In rare cases, when there is much infiltration of the surrounding mucous membrane, the ulceration may extend slightly beyond the confines of the glands. An ulcer from a single Peyer's patch may be five inches long, and the blending of ulcerated patches and follicles in the neighborhood of the ileocæcal valve may affect so large an area, that this part of the intestine may seem to have lost almost all its mucous membrane.

With the sloughing and disintegration of the new tissue the process of infiltration ceases, and hence there is no induration or thickening of the base or edges of the ulcer. The base is smooth, and is usually formed of the submucous or muscular coat of the intestine. The edges are usually thin and undermined, and consist of a well-defined fringe of congested mucous membrane (Fig. 240). This is best seen when the gut is floated in water. In some cases, especially where there is

surrounding infiltration, the edges are firm and thick. In others, again, the sloughing is deeper, and extends through the muscular layer to the peritoneum. The latter may either slough or give way under some muscular effort, either of the bowel when stimulated by improper food, or of the abdominal muscles when the patient is allowed to use them strongly. The perforation is generally small. As a rule, *diffuse peritonitis* (purulent) results: rarely, adhesions form and localize the inflammation. Peritonitis may also occur by simple extension from the gut, from an inflamed gland, or from a splenic abscess. *Hemorrhage* may occur from any vessel opened up during the separation of the slough. It is due either to insufficient plugging by thrombosis or to mechanical displacement of the thrombus after it is formed.

FIG. 240.

A typhoid ulcer of the intestine (diagrammatic), showing the undermined edges of the ulcer and the slough still adherent. *a*, mucous membrane; *b*, submucous tissue; *c*, muscular coat; *d*, peritoneum.

FIG. 241.

A tubercular ulcer of the intestine (diagrammatic). *a*, mucous membrane; *b*, submucous tissue; *c*, muscular coat; *d*, peritoneum.

The third stage of the process is that of **cicatrization**, which usually begins in the fourth week. This takes place by the resolution of the peripheral infiltration, the approximation of the undermined edges and their union with the floor of the ulcer, and the gradual formation of an epithelial covering by growth from the margin. The gland-structure is not regenerated. The resulting cicatrix is slightly depressed and less vascular than the surrounding mucous membrane. It is pigmented either uniformly, or only round the margin. There is no puckering or diminution in the calibre of the gut. In some cases, however, cicatrization does not take place so readily, and the floor of the ulcer becomes the seat of a *secondary* and more extensive ulceration. This may take place after the general disease has run its course, or during a relapse. Profuse hemorrhage and perforation are common results of secondary ulceration. Only one ulcer may be affected by this secondary process, the rest having either healed or being in a fair way to become so.

Comparison between Typhoid and Tubercular Ulceration.—From the foregoing descriptions of typhoid and tubercular (p. 375) ulceration of the intestine, it will be noticed that these two conditions have one important character in common—viz., the uniformity with which *both arise in the lymphoid tissue*. Hence in both cases the ulcers are most marked in the ileum opposite the mesenteric attachment, and may be limited to the Peyer's patches and the solitary glands. There are, however, two characters possessed by tubercular ulcers which generally suffice to distinguish them from typhoid ulcers. The first is the much greater tendency of tuberculosis to spread by means of the vessels, and the second is the presence of outlying tubercles which invariably pre-

cede the advance of the ulceration. Thus, the typhoid ulcer, remaining limited to a Peyer's patch, has its long axis *parallel* to that of the intestine. On the other hand, the tubercular ulcer, often spreading transversely along the vessels before it has involved more than half the patch, has its long axis *at right angles* to that of the intestine, round which it may form a band. Again, as the slough separates, the floor of the typhoid ulcer tends to become cleaner and smoother, and its edges thinner and more undermined. On the other hand, the floor, base, edges, and adjacent peritoneum are, in the case of the tubercular ulcer, always thick and irregular from the presence of developing and degenerating tubercles (Figs. 240, 241).

The Spleen.—In the spleen, the change resembles that which ordinarily occurs in acute febrile diseases, although it reaches its maximum in typhoid fever; but it may be absent, especially in older patients. The splenic vessels are greatly distended and the pulp is crowded with corpuscles. The spleen is consequently enlarged, often attaining two or three times its natural size. Its consistence is fairly firm during the first week, but softer in the second and third. On section, the organ is at first dark-red and opaque-looking; a week later the Malpighian bodies are often prominent and enlarged. Clumps of typhoid-bacilli are found in the spleen, but no local tissue-reaction is discoverable in the neighborhood. Necrotic areas somewhat resembling anæmic infarcts, but not confined to the cortex, are occasionally found. These are probably due to circulatory disturbances and not to the direct action of the bacilli, for in the latter case signs of local inflammation would be present. Large corpuscles, containing two or three normal or altered red corpuscles, may be numerous, and similar cells have been found in the blood. As the fever subsides (fourth week), the hyperæmia diminishes, and some fibrous overgrowth occurs; otherwise the organ regains its normal characters and dimensions.

The Mesenteric Glands.—The change in the mesenteric glands is probably secondary to that in the intestine. These glands become the seat of an acute cellular infiltration, and are enlarged, soft, and vascular. Usually, as in the spleen and many of the glands in the intestine, the inflammation gradually subsides. In rare cases, however, the capsule of the gland is destroyed, and the softened matters may escape into the peritoneal cavity and so cause peritonitis. The enlarged glands may also become caseous and subsequently calcified.

The Marrow.—Ponfick has shown that in typhoid fever the marrow of bones, like the *splenic pulp*, may contain large cells, in which may be as many as twenty-five red corpuscles: these break down, and in the convalescent stage the large cells only contain pigment.

Inflammation of the Appendix Vermiformis.

The vermiform appendage is subject to the same morbid conditions as the rest of the intestines. **Catarrhal inflammation** of the mucous membrane is a common affection: if mild, it may give rise to no serious

trouble; if acute, it may spread to the muscular and serous coats of the organ (*appendicitis*), and thus give rise to local or general peritonitis. Other results of catarrh are blocking of the orifice of the appendix communicating with the cæcum and the formation of concretions within its cavity. (1) When the orifice of the appendix is blocked, owing to swelling of the mucous membrane or to actual stricture due to cicatrization of an ulcer, mucous secretion accumulates behind the obstruction and *distention* of the organ results. Under these circumstances, as in cases of strangulation of a portion of intestine, the Bacillus coli communis, normally present, may develop increased virulence, and may pass through the wall of the distended appendix, reaching the serous surface and setting up peritonitis in the neighborhood (*perityphlitis*). (2) **Concretions** may form within the lumen of the appendix by deposit of earthy salts around a nucleus of desquamated epithelium or inspissated mucus. These concretions may closely resemble foreign bodies, such as grape- or date-stones. In very rare instances actual *foreign bodies* (pins, bristles) may lodge in the appendix; *fæcal material* may also accumulate there and be moulded to the shape of the cavity. As a result of catarrh or of irritation by concretions, **ulcers** may form in the walls of the appendix and perforation may occur. Typhoid fever, tuberculosis, and, in rare instances, actinomycosis may also cause ulceration of this organ.

Gangrene of the appendix may be brought about by very intense inflammation (p. 31), or by cutting off of the blood-supply, owing to torsion of the organ upon its long axis or to acute kinking produced by contraction of its mesentery.

Inflammation of the peritoneum in the neighborhood of the appendix may be of the "dry" type, leading to *adhesion* between neighboring parts, or may result in the formation of an **abscess**, the walls of which are formed by adjacent coils of intestine and the abdominal parietes. If the pus contained in such an abscess be not evacuated it may burst into the cæcum or any other neighboring hollow organ, into the general peritoneal cavity, or through the anterior abdominal wall. In other cases the abscess may burrow behind the ascending colon and reach the under, or even the upper, surface of the liver. In cases of rapid perforation, or gangrene of the appendix, *general purulent peritonitis* may result, sufficient time not being allowed for the formation of adhesions.

Dysentery.

The changes occurring in dysentery are practically limited to the large intestine, and frequently do not extend above the rectum and descending colon, in which parts the disease is always most marked.

Dysentery is a disease mainly characterized by ulceration and sloughing of large areas of the mucous membrane of the intestine.

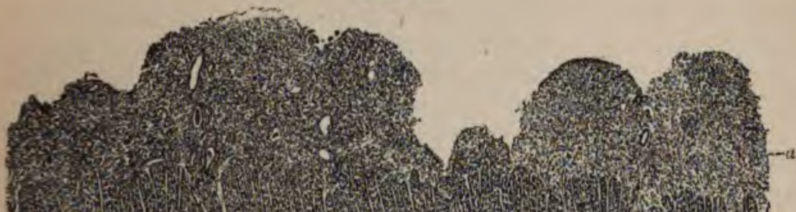
The local changes, however, vary considerably according to the intensity and stage of the disease. In the mildest forms and earliest

stages the changes are most marked on the summits of the folds of the mucous membrane. These are found covered with a grayish-white layer of fibrinous material which, when scraped off, leaves a superficial loss of substance. The mucous membrane, generally, is hyperæmic, softened, and spotted with petechiæ. The submucous tissue also is infiltrated with leucocytes, and the solitary glands are enlarged and prominent.

When the process is more severe, the submucous tissue becomes more extensively involved, and the superficial layer of fibrinous material extends over wider areas, implicating more deeply the mucous membrane. The thickening of the intestinal wall, however, is much greater in some parts than in others, so that projections are produced upon the inner surface of the intestine corresponding with those parts which are the most affected. The enlarged solitary glands usually slough, giving rise to circular ulcers, which rapidly increase in size. By the time the process has reached this stage, the muscular and serous coats have become implicated, the latter being covered with a layer of fibrin which forms adhesions to adjacent parts. The intestine is much dilated, and contains blood and disintegrating inflammatory products.

In the most severe forms of this disease the necrosis is still more extensive. Large portions of the mucous membrane are converted into black rotten sloughs, and the submucous tissue is infiltrated with hemorrhagic exudation; this is generally followed by suppuration, by means of which the necrosed portions of tissue are removed (Fig. 242).

FIG. 242.



Ulceration of descending colon from a case of chronic dysentery, from a patient who died of pyæmic abscesses in the liver. The submucous tissue is extensively infiltrated and ulcerated, while all trace of the mucous membrane has disappeared. *a*, ulcerated submucous tissue; *b*, circular muscular layer; *c*, longitudinal muscular layer; *d*, connective tissue. × 12.

If the inflammatory process subsides before death occurs the ulcers (Fig. 243) may gradually heal. When the loss of substance has not been considerable the edges of the ulcers may, by the contraction of the submucous tissue, become completely approximated. More commonly, however, the loss of substance is so great that large portions of

the interior of the intestine are left uncovered, save by fibrous tissue and islets of mucous membrane.

When the inflammatory process becomes chronic the changes in the submucous connective tissue become more marked, and the new fibroid growth gives rise to considerable thickening and induration of the

FIG. 243.

Ulceration of large intestine in chronic dysentery. *a*, islets of ulcerated mucous membrane and thickened submucous tissue; *b*, muscular coat of intestine; *c*, deep ulcer exposing peritoneal coat. Natural size.

intestinal wall, and to contraction and narrowing of the lumen. Sometimes fibrous bands are formed, projecting into the gut. Abscesses and fistulous passages not infrequently occur in the thickened intestinal wall.

The etiology of dysentery is imperfectly known. By some it is attributed to the presence of amœbæ (p. 257), by others to bacteria. Not improbably both these agencies are capable of producing allied, if not identical, conditions.

Extensive ulceration of the colon (*ulcerative colitis*) is sometimes met with in temperate climates, and is often looked upon as distinct from true dysentery. Epidemics of this disease have occurred not infrequently in asylums; they appear to be due to a special bacillus, probably identical with that found by Shiga in some cases of tropical dysentery.

Tumors of the Stomach and Intestines.

Stomach.—Primary carcinoma is the only new-growth frequently found in the stomach. In the male the stomach is the commonest seat of primary cancer, but in the female both breast and uterus are more frequently affected. The form of cancer found varies, to some extent,

with its position. At the pylorus, which is affected in two-thirds of the cases, scirrhus, encephaloid, or even columnar epithelioma may be found. At the cardiac end, squamous epithelioma is not infrequent, while all forms are liable to undergo colloid degeneration. In whatever part of the organ the cancer arises, it spreads most rapidly in the submucous layer, but always involves, to some extent, the muscular coats. As it extends it gives rise, in the interior of the organ, to fungating masses (Fig. 244) or to ulcers with hard edges and rough floors; and on the exterior, to adhesions to neighboring organs, due

FIG. 244.

Carcinoma of pyloric end of stomach. *a*, mucous membrane of stomach; *b*, thickened and contracted wall of stomach due to presence of new-growth; *c*, everted pyloric valve; *d*, duodenum.

to the direct spread of the growth. Secondary growths in the glands and liver are exceedingly frequent. When situated at the pylorus, the growth causes thickening and eversion of the valve into the duodenum, and narrowing of the orifice, leading to marked dilatation of the stomach at a comparatively early stage of the disease. The secretion of hydrochloric acid by the gastric glands is usually diminished or arrested in cases of cancer; but this functional defect is found also in other morbid conditions of the stomach.

Intestine.—Two varieties of new-growth are commonly found in the intestine—*adenoma* and *carcinoma*.

Intestinal adenomata are generally polypoid in form. The glandular elements in the mucous membrane covering them are often so little

increased that some of the tumors may with equal correctness be classified as *papillomata* or *fibromata*. They are found in both small and large intestine.

Almost every form of carcinoma may occur primarily in the intestine, but *columnar epithelioma* is certainly the commonest. The growth invades the submucous and muscular walls, but mainly projects into the interior, rapidly encircling, and seriously narrowing, the lumen of the intestine. Carcinoma of the intestine is a common cause of chronic intestinal obstruction in old people. The rectum, the flexures of the colon, and the cæcum are the commonest parts involved. Secondary growths occur in the mesenteric glands and in the liver, sometimes before any symptoms have been produced by the intestinal growth. The peritoneum may be involved by direct extension or by metastasis.

IV. DISEASES OF SEROUS MEMBRANES.

The phenomena of inflammation affecting serous membranes vary with the nature and intensity of the irritant to which the condition is due. It is convenient to distinguish three varieties of cases: (1) The so-called "dry" cases, in which little exudation occurs; (2) those accompanied by free escape of serous or serofibrinous effusion; and (3) those in which the fluid poured out is purulent.

(1) *"Dry" or "Plastic" Inflammation.*—The sequence of events constituting inflammation is the same in serous membranes as in other vascular parts, comprising dilatation of the bloodvessels, alteration in the characters of the blood-stream, exudation of fluid, and escape of leucocytes and occasionally of red corpuscles. The earliest visible sign of inflammation is hyperæmia, shortly followed by a loss of the natural polish of

FIG. 245.

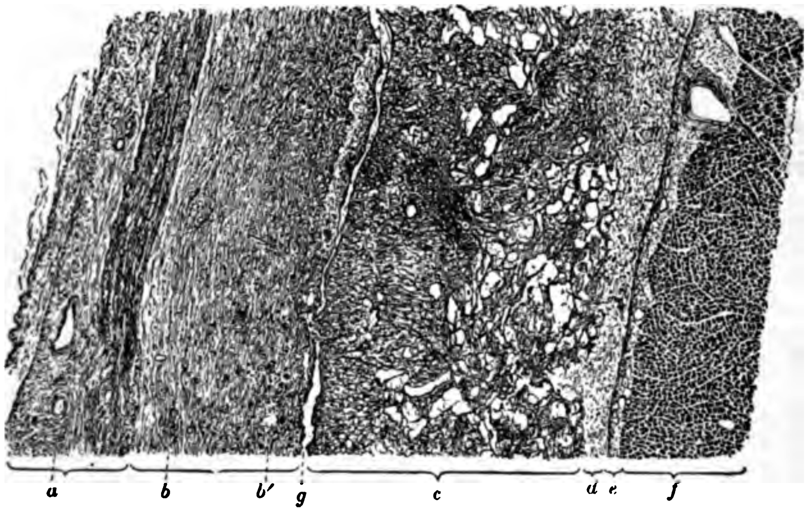
Inflamed omentum of a rabbit, showing changes in the endothelium. × 250. (Cornil and Ranvier.)

the endothelial surface. The cells of the endothelium become swollen and granular; they multiply rapidly, and many cells, injured by the irritant, are cast off from the surface (*desquamation*) (Fig. 245). At the same time leucocytes escape from the vessels and infiltrate the subendothelial tissue, some escaping on to the actual surface, accompanied by a slight exudation of fibrinous lymph, which forms a white or yellowish-white layer, more or less closely adherent to the damaged

endothelium. This deposit of lymph tends to accumulate at points where pressure is least, as in the angles between adjacent coils of intestine. Microscopically, the exudation is seen to consist of a network of coagulated fibrin containing within its meshes numbers of emigrated leucocytes.

As the inflammation subsides, the hyperæmia diminishes, and more or less adhesion takes place between the roughened surfaces of the serous membrane where they are in contact. The connective-tissue cells multiply and shoot processes into the layer of fibrin, which is gradually absorbed; new vessels are formed in this connecting mass, and complete union by fibrous tissue thus takes place (Fig. 246).

FIG. 246.



Fibrinous pericarditis of two weeks' duration. *a*, parietal pericardium with artery and vein; *b*, organizing layer of fibrin, with engorged vessels appearing as dark points on its visceral edge (*b′*); *c*, fibrinous mesh-work; *d*, organizing layer adjoining visceral pericardium (*e*); *f*, muscular wall of heart with subpericardial fat and vessels; *g*, line of union of the two inflamed surfaces, showing that by far the larger amount of fibrinous exudation is on the visceral side. × 6.

Owing to the movements of the opposing surfaces one upon another it often happens that the newly formed fibrous connections are pulled out into threads or bands of varying thickness. In this way are formed the peritoneal bands, which are important as a possible cause of subsequent intestinal obstruction, and the curious shaggy condition of the pericardium occasionally resulting from inflammation (*cor hirsutum*).

(2) *Serous Inflammation.*—The hyperæmia and roughening of the serous surface takes place in this as in the previous case, but the effusion of fluid from the vessels is much greater, and widely separates the usually contiguous surfaces, forming a large cavity bounded by the serous membrane. In many cases scarcely any lymph coagulates on

the endothelium, and the effusion remains fluid and almost clear. In other instances a layer of lymph is deposited on the walls of the cavity, and the fluid itself contains flakes of coagulated fibrin (*sero-fibrinous effusion*). In the latter cases the fluid may coagulate to a jelly-like substance when withdrawn from the body. Occasionally the escape of red blood-corpuscles is so free that the fluid is more or less deeply blood-stained (*hemorrhagic effusion*). Subsidence of the inflammation is followed by absorption of the effused serum through the veins and lymphatics. In cases in which the effusion is very large, and the pressure produced upon the walls of the cavity correspondingly great, such absorption is hindered by the resulting compression of these vessels, and it may be necessary to withdraw artificially some of the fluid so as to diminish the tension and allow natural absorption to occur. When the fluid has disappeared, union of the opposed surfaces of the serous membrane will take place, as in the previous instance, wherever the endothelium is sufficiently damaged.

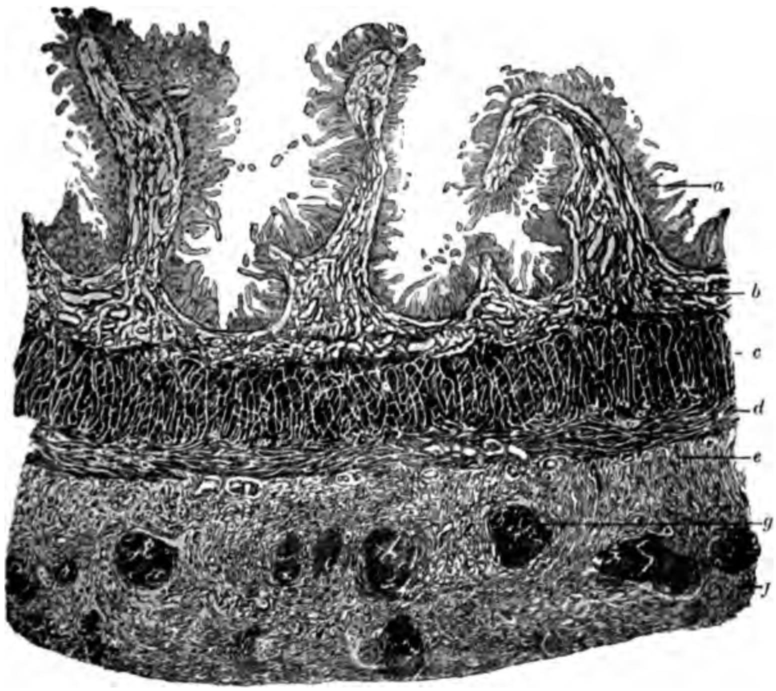
(3) *Purulent Inflammation.*—In certain cases the nature of the irritant is such that it exercises a chemotactic influence on the leucocyte and causes a very free exudation of these cells into the serous cavity. The effusion will then be purulent or seropurulent, according to the proportion of leucocytes and fluid which escapes. Such purulent effusions do not tend to undergo spontaneous absorption, and must be artificially evacuated. If the pus remains in the serous cavity for any length of time, great thickening of the serous membrane occurs, as a result of the chronic inflammation existing in the subendothelial tissue; the endothelial cells, to a great extent, disappear, and the cavity is lined with granulation-tissue throughout. Obliteration of the cavity takes place, as above, when the walls are allowed to come into contact.

Etiology.—Inflammation of serous membrane is generally the result of the presence of pathogenic organisms, which may be admitted either (1) by direct traumatism (penetrating wounds, rupture of viscera) or (2) by means of the blood-stream or lymphatics. The bacteria generally found in cases due to traumatism are the common pyogenic cocci, or the Bacillus coli communis: in the second class of instances, the pneumococcus, the bacilli of tuberculosis and of glanders, and rarely the gonococcus, may be responsible for the condition.

Exposure to cold was formerly considered to be an exciting cause, and the possibility of such an occurrence is not absolutely disproved. It may undoubtedly act as a predisposing condition, rendering the tissues unable to resist bacteria accidentally present. The frequent occurrence of inflammation of serous membranes in diseases of the kidney shows that the poisonous substances circulating in the blood in such conditions act as exciting causes of this form of inflammation, or that resistance to the bacterial infection is diminished—possibly by disappearance of the normal alexines. Serous membranes may be involved secondarily by extension of inflammation from the viscera which they invest, as happens to the pleura in cases of pneumonia,

or to the peritoneum over a gumma in the liver or over an ulcer of the intestine.

FIG. 247.



Small intestine, showing chronic tubercular peritonitis. *a*, normal mucous membrane; *b*, submucous tissue; *c*, circular muscular layer; *d*, longitudinal muscular layer; *e*, thickened subperitoneal tissue; *f*, chronic inflammatory tissue undergoing caseation near the free edge; *g*, caseated foci. × 12.

The same irritant cause is capable, under different conditions, of producing all the varieties of inflammation here distinguished. An example may be seen in the inflammation of the peritoneum due to the Bacillus tuberculosis (*tubercular peritonitis*). The simplest form consists in the deposit of a number of miliary tubercles in the subperitoneal tissue, as may frequently be seen over a tubercular ulcer. These tubercles may be scattered throughout the whole of the peritoneum. As the process advances, a dry fibrinous exudation may become the most prominent feature and the coils of intestine may be subsequently matted together by fibrous tissue (Fig. 247). In other instances a large serous effusion takes place into the peritoneal cavity (*ascites*); and, very rarely, a true suppurative peritonitis may be produced. It is possible, however, that in these last cases other organisms may aid the Bacillus tuberculosis in producing the suppuration.

Effects.—Simple dry inflammation of serous membranes is accompanied by considerable pain, owing to the friction between the inflamed

surfaces. Large serous effusions embarrass the action of the neighboring viscera, as of the heart in pericardial effusion, or of the lung in pleurisy: in the latter case collapse of the lung may take place owing to the pressure of the fluid. In very chronic conditions, as in purulent pleurisy (*empyema*), the fibrous tissue, formed by the union of the opposing surfaces, may subsequently, by its contraction, cause some local falling in of the chest-wall and consequent deformity. The inflammatory process may extend from the serous membrane into the substance of the underlying organs, as is seen in the myocarditis which results from pericardial inflammation, and in the interstitial pneumonia which follows chronic pleurisy; this fibrosis of the lung takes part in producing the retraction of the chest just alluded to (see Bronchiectasis). In peritonitis the extension of the inflammation into the muscular coat of the gut leads to paralysis of the muscle and consequent distention of the intestines (*tympanites*).

In the case of the pericardium, the obliteration of the cavity by adhesions (*adherent pericardium*) results in throwing additional work on the heart, the contraction of which is impeded. Great hypertrophy of the heart may be produced to compensate for this impediment. In a few cases the tightness of the coat of fibrous tissue formed around the organ is such that no enlargement can occur, and cardiac failure is an early and necessary result.

The fibrous material produced in tubercular peritonitis may be unevenly distributed, giving rise to irregular masses of matted intestine or omentum. Caseation occurs in the new tissue, resulting in the formation of collections of puriform material (Fig. 247). These "cold abscesses" may burst either into the intestine or through the abdominal parietes: if perforation occurs in both directions, a *fæcal fistula* will result. Movement of the intestines is prevented by the fibrous adhesions between the coils, and obstruction of the lumen of the gut may occur as the result of kinking produced by contracting adhesions.

It is worthy of note that the adhesion of the two surfaces of a serous membrane resulting from inflammation is, in many cases, a *protective condition*. Thus fusion of the pleural surfaces over a tubercular vomica prevents the possibility of the ulcerative process extending into the pleural cavity with consequent pneumothorax, while adhesions around a gastric or intestinal ulcer are protective against perforation and resulting general peritonitis.

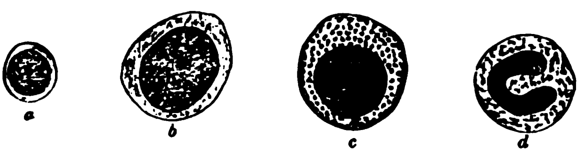
V. DISEASES OF THE BLOOD.

Normal blood contains on an average 5,000,000 red corpuscles, and from 7000 to 10,000 leucocytes, in every cubic millimetre. Its specific gravity is approximately 1055. The great majority of the leucocytes present in normal blood are of the polynuclear variety (Fig. 248); these constitute about 70 per cent. of the whole number. Small uninuclear leucocytes (*lymphocytes*) form about 20 per cent., large hyaline leucocytes and eosinophile cells each about 5 per cent. of the

total. Leucocytes with basiphile granules are rarely present in normal blood.

In disease the number of the red corpuscles and their hæmoglobin-content are frequently diminished (*anæmia*). Along with these changes, alterations are met with in the shape and size of the red corpuscles, by which large corpuscles (*megalocytes*), small corpuscles (*microcytes*), and nucleated corpuscles (*normoblasts*) are produced. Irregularly shaped corpuscles may at times occur (*poikilocytosis*). Considerable increase in the number of red corpuscles (*polycythæmia*) is occasionally met with, especially in congenital heart-disease. The amount of hæmoglobin contained in each corpuscle may be greater or less than the normal amount. The number of the leucocytes may also vary. These cells are diminished in number (*leucopenia*) in typhoid fever and in a few other infective diseases; increased (*leucocytosis*) in most infective diseases, especially in pyogenic infections, and very greatly increased in the disease known as leucocythæmia. The relative numbers of the different varieties of leucocytes may also be altered in disease. Increase in the number of eosinophile cells (*eosinophilia*) is especially associated with the presence in the blood of animal parasites

FIG. 248.



Leucocytes from normal blood: *a*, lymphocyte; *b*, hyaline leucocyte; *c*, coarsely granular leucocyte; *d*, finely granular leucocyte.

(trichina, ankylostoma, bilharzia). Alteration in the density of the blood may at times occur; thus the specific gravity of the serum is low in chronic Bright's disease, and that of the blood as a whole in chlorosis, owing to lack of corpuscles. The coagulation time of the blood may also be shorter or longer than normal. In certain conditions the blood may contain excess of fat (*liphæmia*); this is generally associated with diabetes.

Anæmia.

The term "anæmia" has no very definite connotation. As generally employed, it includes all diseases of the blood which are characterized by a deficiency in the number of the corpuscles or a diminution in the total percentage of hæmoglobin. Other terms with a more precise significance are sometimes used. Thus a diminution in the number of red corpuscles is known as *oligocythæmia* or *aglobulism*, and a deficiency in the hæmoglobin as *achromatosis*. These results may be produced in many diseases (*secondary anæmia*). Thus, anæmia is common during convalescence from acute fevers and after severe hemorrhages. It is an invariable attendant in Bright's disease, lead-

poisoning, and many chronic exhausting illnesses. It may also owe its origin to deficiencies in the food, or to conditions which produce the same practical result—stricture of the œsophagus or of the pylorus. In cases due to these causes the number of red corpuscles is always reduced, while the leucocytes may be either slightly diminished or slightly increased. Not only is the total percentage of hæmoglobin below the average, but the amount contained in each corpuscle is less than normal. Anæmia following acute fevers or hemorrhage rapidly disappears: the exact rate of disappearance varies with the nature and severity of the disease, the recuperative power of the patient, and the general conditions of convalescence.

To two varieties of **primary anæmia** special reference must be made: these are (1) *Chlorosis*, and (2) *Pernicious Anæmia*.

1. Chlorosis.—Chlorosis is mainly a disease of girls and young women. It takes its name from the effects of its most marked feature, the pallor due to the *deficiency of hæmoglobin*. This is so great that the skin and mucous membranes of the patient often assume a very pale greenish tinge. In extreme cases the hæmoglobin may fall to one-eighth of its full amount, and in most it is less than a third. The *fall in red corpuscles*, though considerable, is by no means parallel. In mild cases they may average 3,500,000 to the cubic millimetre, and they seldom fall below 2,000,000. The corpuscles are, on the whole, distinctly smaller than usual. Some of them are very small, ranging down to 3 μ in diameter (*microcytes*); a few are large, with a diameter up to 12 μ (*macrocytes*); while others with an irregular outline are occasionally found (*poikilocytes*). The *specific gravity* of the blood may fall ten to twenty degrees, owing to the corpuscular defects, for the density of the plasma is unchanged. Some authorities maintain that the total quantity of red corpuscles is normal in chlorosis, but that the blood is increased in quantity by excess of fluid plasma, so that less corpuscles are contained in a measured volume than in the case of normal blood. In some few cases, where death has occurred, the heart and large arteries have been found unusually small. Other morbid conditions, secondary to the changes in the blood, may coexist. Among these are dyspnœa and the occasional deposit of subcutaneous fat, both resulting from the deficient oxygen-carrying power of the blood; slight œdema, probably from defective nutrition of the vessel walls; and various auscultatory signs due to the defective action of the walls of the inadequately nourished heart and large vessels, combined, according to some authorities, with the lowered specific gravity of the blood. There is a tendency to the occurrence of venous thrombosis, and in severe cases optic atrophy may occur.

Pathology.—No explanation of the changes in the blood has yet been generally accepted, though many have been suggested. It is very generally believed that chlorosis is due to defective blood-formation (*hæmogenesis*), and not to increased blood-destruction (*hæmolysis*), for the evidences of the latter, which are readily found in pernicious

anæmia, are absent in chlorosis. Virchow first drew attention to the small size of the heart and large arteries, and attributed it to defective development. He regarded the disease as the expression of an inability of the blood-forming organs to meet the demands made upon them during a period of rapid development—a disease especially liable, therefore, to occur in those in whom these parts are congenitally defective. The great frequency of the disease, its practical limitation to one sex, and its ready curability point, however, to a more transient and less organic causation.

It is unquestionable that gastralgia, gastric catarrh, gastric ulcer, *constipation*, defective hygienic surroundings, and irregular habits are frequently associated with the condition; and that in many examples of the disease the administration of iron fails to effect a cure until these are relieved. On the other hand, it is no less certain that the relief of these conditions without the administration of the iron is ineffectual as a cure, and that an adequate diet contains an appreciable amount of that metal. It is also well known that hæmoglobin, which contains iron, is the progenitor of pigments containing none; and that the amount of this metal normally excreted in the fæces and the urine is excessively small, and is not appreciably increased in anæmia. It seems reasonable to suppose that the iron thus retained within the body is utilized in the formation of hæmoglobin; and if, therefore, the hæmoglobin in the blood is deficient it would seem more rational to look for *a cause that interferes with the synthesis of hæmoglobin* from the accumulating stock of iron, rather than for one which leads to any loss in the total amount of iron contained in the body. Although in some cases menorrhagia precedes the onset of chlorosis, this sequence is unusual, and the loss in hæmoglobin is generally more marked in chlorosis than in anæmia due to hemorrhage.

It must be confessed that the cause of the defective hæmogenesis is at present unknown. By some it is attributed to a deficiency of iron-containing foods, combined with an increased loss of iron due to the recurrent hemorrhages occurring in menstruation (Stockman); by others, to intestinal decompositions interfering with the absorption of iron (Bunge, Landwater); and by others, again, to some error in the internal secretion of the ovary (Van Noorden, Arcangeli).

2. Pernicious Anæmia.—Pernicious anæmia differs from chlorosis in many important particulars. It occurs in older persons and in males, and is, moreover, generally fatal. Sometimes the disease seems to follow severe hemorrhage after childbirth or any of the ordinary antecedents of anæmia already mentioned. More often it has no obvious cause.

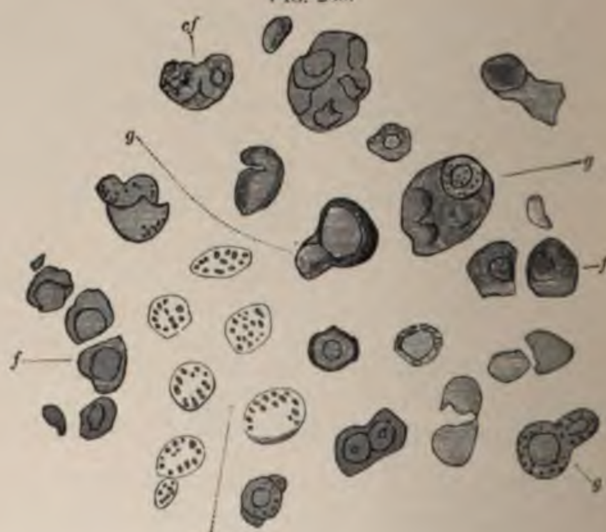
The blood in pernicious anæmia is very different from that in chlorosis. It differs from it in three important particulars: (1) The most marked feature in pernicious anæmia is the *diminution in the number of red corpuscles*. Thus, although the total amount of hæmoglobin is invariably diminished, yet the amount contained in each cor-

puscle may even be in excess of the normal. A fall in the percentage of red corpuscles to 1,000,000 in the cubic millimetre is not uncommon, and blood with only 143,000 has been described. (2) The next most characteristic difference is the frequency of *changes in the form and size of the corpuscles.* Sometimes there are found, as well as normoblasts, enormous nucleated red corpuscles (20 μ dia.) known as megaloblasts (Fig. 249). According to Eichhorst, the microcytes are not only much more numerous than in chlorosis, but have a very characteristic appearance. They are spherical, granular, and highly pigmented. Poikilocytosis is an almost constant phenomenon. The number of leucocytes and of blood-platelets is somewhat diminished, the tendency to the formation of rouleaux is less marked, and the coagulating-power of the blood is feebler. Granules, supposed to represent the disintegration of red corpuscles, are sometimes found. (3) *The total quantity of blood is markedly diminished.* At a post-mortem examination the vessels are almost empty. If this fact be considered in connection with the per-

FIG. 249.

Blood-corpuscles showing poikilocytes (*p*), microcytes (*m*), and nucleated corpuscles (megaloblasts) (*n*). (Mott.)

FIG. 250.



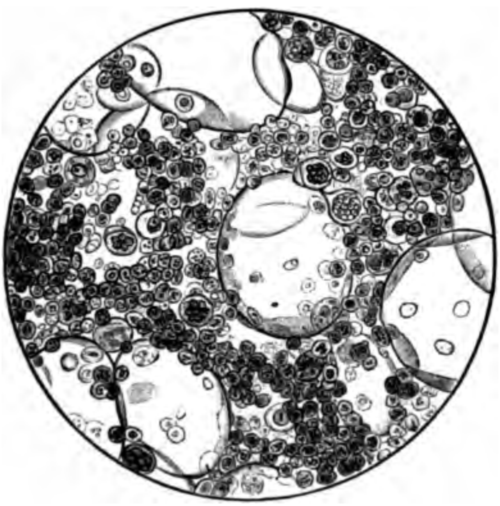
Pernicious anæmia. Fresh marrow from humerus treated with Hayem's fluid and teased. Ordinary marrow-cells are shown (*o.m.c.*). The shaded cells are pigmented marrow-cells forming blood-corpuscles; the larger are megaloblasts and the smaller normoblasts. The cells marked (*f*) show multiplication by fission, those marked (*g*) multiplication by gemmation. (Mott.)

centage fall in red corpuscles and the slightly diminished specific gravity of the blood-serum (1026), some idea can be formed of the enormous extent of the change, so far as the blood is concerned.

The **marrow** of the long bones is generally red and contains less fat than normal. Large numbers of megaloblasts are found, and there is also an increase of normoblasts, and often of microcytes. (Figs. 250, 251). The red marrow contains pigment giving the iron reaction (see below). The finer bony trabeculæ may become absorbed.

The changes in the **liver** are of considerable importance. In the centre of the lobule there may be an excess of *pigment*, and, in the peripheral zone, of *iron*, so loosely combined with organic matter that a distinct blue coloration can be obtained on treating sections of the organ with ferrocyanide of potassium and dilute hydrochloric acid.

FIG. 251.



Pernicious anæmia. Same marrow as in Fig. 250, but hardened in Müller's fluid and cut in celloidin. Some half-dozen fat-vesicles are seen, with the intervening capillaries much dilated. These contain normoblasts with rosetted nuclei. The smallest cells are microcytes; those of intermediate size are granular-looking red corpuscles. (Mott.)

The cells in the immediate neighborhood of the intralobular veins are occasionally fatty.

The **heart** and smaller bloodvessels, and occasionally the intima of the large arteries, show extensive fatty changes, from which the skeletal muscles are practically free. The changes in the heart are particularly well marked. In the left ventricle the fatty areas are so distinct that the terms "thrush-breast" and "tabby-cat" have been used to denote the mottled appearance produced. The **subcutaneous fat** is very generally increased. The **skin** acquires a faint yellowish or "old-wax" color, suggestive of slight jaundice. Small *hemorrhages* are common in many parts. Flame-shaped hemorrhages in the **retina**, clustered round the disk, are particularly frequent and are an important aid to **diagnosis.** Exacerbations are accompanied by fever. The **urine** is

generally dark, and an excessive amount of urobilin is excreted. In the **spinal cord** degenerative changes have been observed in the posterior and lateral columns, as well as peri-arteritis, and hyaline changes in the spinal capillaries.

Pathology.—Besides the differences above mentioned, which may be held to distinguish chlorosis from pernicious anæmia, additional evidence is gained by observing the effects of the administration of iron. This drug, which effects a cure in chlorosis, is generally useless in pernicious anæmia.

The increase of iron in the liver and marrow, and of urobilin in the urine, affords evidence that the disease is due to the excessive destruction of red blood-cells—hæmolysis. The changes in the marrow of the long bones and the existence of nucleated corpuscles in the blood afford no argument against this view, as they might be due to increased physiological, not to pathological, hæmogenesis. This explanation is the more probable, as repeated bleedings of animals produce similar effects. A condition somewhat similar to that found in the liver in cases of pernicious anæmia has been produced by the administration of toluylene diamine. This discovery led to the suggestion that the disease is due to the absorption of toxic products from the intestine. Two observers have described special organisms in the blood, but their results have not yet been confirmed. Hunter has found streptococci in the stomach in several cases of pernicious anæmia, but it is not certain that these were not merely instances of "terminal infections." Many organisms, however, give rise to toxines which have a destructive effect upon blood-corpuscles (*B. tetani, streptococci*), and the possibility of an infective cause for this disease is worthy of careful investigation. The presence of the Bothriocephalus latus in the intestine may also be accompanied by symptoms of pernicious anæmia, which disappear when the parasite is removed. The recent discoveries with regard to the process of hæmolysis have not as yet been followed by any new light upon the causation of pernicious anæmia. Some authors deny that the disease is due to destruction of blood-corpuscles, and attribute it to defective formation of blood (Bloch, McFarland).

The changes in the spinal cord have been attributed (1) to degeneration after hemorrhage, (2) to focal myelitis and its results, and (3) to the cause producing the anæmia. Attempts to produce the changes experimentally have failed.

It is worthy of note that while in phosphorus-poisoning the fatty degeneration is almost universal, in pernicious anæmia it is far more marked in the heart than elsewhere. Mott has suggested that, while the feeling of languor, so characteristic of the disease, imposes rest upon the skeletal muscles, the deficient quantity and diminished oxygenating capacity of the blood necessitate increased work on the part of the heart. The balance of work and repair in the organ cannot, therefore, be maintained, and degeneration ensues to a greater extent than elsewhere.

Leucocythæmia.

Leucocythæmia, or leuchæmia, is a disease characterized by a considerable increase in the number of white corpuscles in the blood, by a diminution in that of the red corpuscles, and by changes in the spleen, lymphatic glands, bone-marrow and other organs.

Leucocytosis.—In some conditions a slight increase in the number of white corpuscles occurs without any other change, and is termed "leucocytosis." This differs from leucocythæmia in that the increase in white corpuscles is limited to the multinucleated leucocytes (Figs. 100 and 248), and is unattended by anæmia or any of the other changes characteristic of leucocythæmia. Leucocytosis occurs, physiologically, after a meal, and in the later months of pregnancy. In septicæmia and pyæmia, and in most of the acute infectious diseases, there is a marked increase of white corpuscles. This increase is probably beneficial, since, as was previously mentioned, leucocytes contain the alexines necessary for the destruction of bacteria. Thus in acute pneumonia the prospect of recovery is smaller if leucocytosis is not present. It is noteworthy that in tubercular affections the leucocytes found in serous effusions are chiefly of the uninuclear variety, and in the early stages of small-pox there is a uninuclear leucocytosis in the blood. It would appear that different toxines give rise to an increase of different varieties of leucocytes. After large losses of blood there is also some degree of leucocytosis.

Cases of **leucocythæmia** may generally be grouped into one of two varieties—*the spleno-medullary* and the *lymphatic*. (1) In the **spleno-medullary** form (*myelocythæmia*) the enlargement of the spleen is very marked, while the lymphatic glands are but little affected. The changes in the blood, which will be presently described, are also more or less characteristic. (2) The **lymphatic** form (*lymphocythæmia*) is usually characterized by an enlargement of the lymphatic glands and by the large number of lymphocytes in the blood.

FIG. 252.

Blood from a case of leucocythæmia (unstained). × 200.

Blood.—The increase in the number of white corpuscles varies considerably in different cases. A proportion of one white to ten red is quite common, and often there are as many as one to three (Fig. 252). In the course of the disease the proportion may for a time fall to normal. The excess of leucocytes gives to the blood a paler and more opaque appearance than natural (*leuchæmia*.)

In the *spleno-medullary* form the excess of white corpuscles is found to be made up of the following varieties of cells: (1) Large uninucleated neutrophile cells resembling marrow-cells (*myelocytes*); (2) large uninucleated eosinophile cells; and, to a less extent, (3) ordinary so-called multinucleated leucocytes, and (4) leucocytes with coarse granules staining deeply with methylene blue (Fig. 253).

Nucleated red corpuscles, suggestive of normoblasts, are also found in considerable numbers; and, according to Muir, the blood-platelets are increased. In the *lymphatic* form the excess of white corpuscles consists almost wholly of lymphocytes.

It is often stated that in leucocythæmia the new corpuscles show no movements when examined on the warm stage. The explanation of this is, that the large majority of the new cells are not such as, under any circumstances, possess the power of amœboid movement. Those leucocytes which show amœboid movements in health do not fail to exhibit them in leucocythæmia.

Fig. 253.

Blood from case of spleno-medullary leucocythæmia. *a*, nucleated red corpuscle; *b*, coarsely granular eosinophile leucocytes; *c*, finely granular multinucleated leucocytes; *d*, myelocytes; *e*, lymphocytes; *f*, red corpuscles. × 1000.

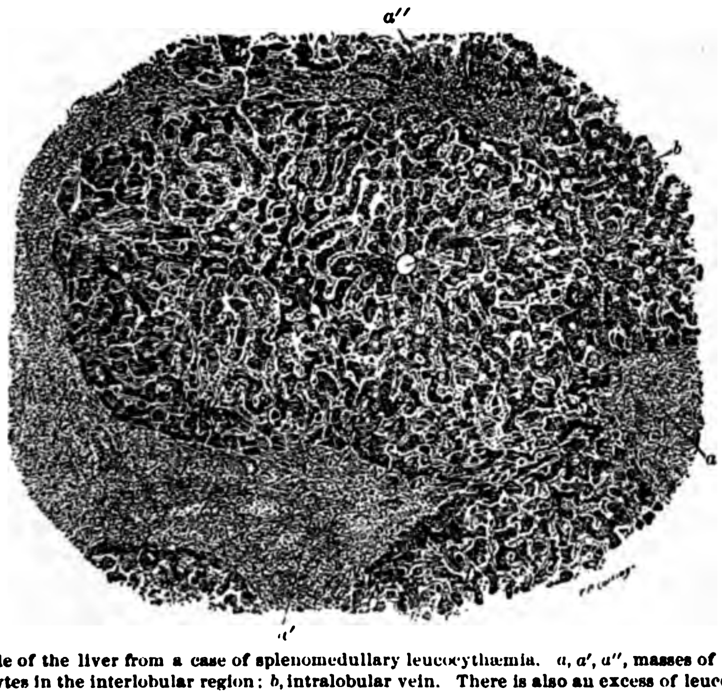
The red corpuscles may be reduced to a half or to a quarter of the normal number. They are usually normal in appearance, but vary both in size and shape. Small, slender, colorless, octohedral crystals containing phosphoric acid have been discovered in the blood, liver and spleen (Charcot's crystals). The coagulating power of the blood in leucocythæmia is much diminished; and when this liquid is allowed to stand, the white corpuscles form a creamy layer upon its surface. There is also *a marked tendency to hemorrhage* into the viscera and, less frequently, from the mucous membranes.

Spleen.—This organ is symmetrically enlarged, often to an enormous extent. The capsule is irregularly thickened, and there may be adhesions to the adjacent viscera. In all chronic cases the con-

sistence of the spleen is firmer than normal, owing to an increased thickness of the reticulum. The organ is closely packed with cells similar to those found in the blood, and the Malpighian corpuscles are generally indistinct: very rarely they may form prominent growths. Except for infarctions, which are common, and may be seen in all stages and varieties (p. 219), the cut section is generally of a uniform reddish color. Phlebitis of the splenic vein with leucocytic emboli in the liver has been found.

Lymphatic Glands.—Enlargement of the lymphatic glands is uncommon in splenomedullary leucocythæmia. In the lymphatic form they are generally much enlarged. Their consistence is usually normal, and

FIG. 254.



Lobule of the liver from a case of splenomedullary leucocythæmia. *a*, *a'*, *a''*, masses of leucocytes in the interlobular region: *b*, intralobular vein. There is also an excess of leucocytes between the rows of fatty liver-cells. × 90.

they are freely movable. On section, hemorrhagic areas are often to be seen. Microscopically the enlargement of the glands is found to be due to an accumulation of leucocytes.

Bone-marrow.—This is of a uniform pale pink color. Microscopically, there is no characteristic change, all the constituents found in leucocythæmia being sometimes found in other conditions. In the lymphatic variety lymphocytes are abundant (Muir).

Generally speaking, lymphoid tissue in any part—*e. g.*, the follicles of the intestine—may be found increased, while any organ may contain foci of leucocytes (Fig. 254) or evidence of local hemorrhage.

Recent chemical observations on the metabolic changes occurring in leucocythæmia point to an increase of xanthin bases in the blood. Most of the changes described are explicable on the theory of the destruction of an unusually large number of leucocytes. There is often excess of uric acid in the urine, due to the same cause.

Lymphatic leucocythæmia generally runs a more rapid course than the spleno-medullary form, and this variety, like acute Hodgkin's disease, may prove fatal in less than two months, while the spleno-medullary form may take more than two years to reach a fatal termination.

Pathology.—The pathology of leucocythæmia is still obscure. It is highly probable that the increae in the number of white corpuscles is due to excessive formation of these cells. Those present in the spleno-medullary forms are, under normal conditions, found in the marrow; and the lymphocytes, occurring in the lymphatic form, may be derived from the lymphatic organs. In this form of the disease the normal bone-marrow is often replaced by lymphoid tissue, which may constitute another source of these cells. The other phenomena of the disease may be accounted for by the accumulation of the cells thus formed in the different organs of the body, and by their consequently increased disintegration. The anæmia may be due to the interference with the normal blood-forming functions of the bone-marrow. According to this view, the enlargement of the spleen is a secondary condition, and depends, according to Muir, partly upon its passive distention with the new cells, and partly—assuming that leucocytes normally undergo disintegration in this organ—on the increased efforts made by the spleen to deal with the abnormal supply of leucocytes.

The cause of the increased proliferation is altogether a matter of conjecture. Many observers have searched for parasites, but none has been definitely associated with the disease. There is, however, an obvious analogy, especially in the case of the lymphatic form, with sarcoma and the peculiar form of sarcoma called chloroma is apparently related to leucocythæmia. In both there is a purposeless growth of cells, which in leucocythæmia are itinerant, and in sarcoma stationary. It is possible to explain, on this analogy, the accumulation of the cells in those places where they are actually found in leucocythæmia.

Splenic Anæmia.

This term is applied to a clinical condition characterized by progressive anæmia of the chlorotic type, by enlargement of the spleen, fever, and by a marked tendency to slight hemorrhage. There is occasionally slight lymphocytosis. Fibrosis is the principal change in the spleen. The pathology of the disease is quite unknown.

Purpura, scurvy, and **hæmophilia** are clinical conditions which, to some extent, resemble pernicious anæmia, splenic anæmia, and leucocythæmia in the tendency each disease shows to hemorrhage; but their pathology is not sufficiently understood to justify any detailed description in this place.

VI. DISEASES OF THE HEART.

Malformations.

In general terms, malformation of the heart comprises the following principal defects—singly or in combination : (1) deficiencies in the septa, (2) dilatation or narrowing of the pulmonary and aortic orifices, (3) redundancies or deficiencies in the valves, (4) persistence of fœtal channels, and (5) transposition of the arterial trunks and other parts.

The *septa* may altogether fail to appear, or their formation may be arrested at any stage of their development. The *entire absence* of any one of these septa produces the earliest forms of malformation. In this way there may be produced a heart with a single auricle, a single ventricle, and a single arterial channel, supplying both systemic and pulmonary circulations, as in fish. If the defect is less extensive, a heart with two auricles, but with a single ventricle and a single artery, may result, as in the frog. These and other corresponding varieties are rare. In all of them extra-uterine life is only possible for a few days. *Incomplete formation* of septa is, however, a more frequent malformation. In this way many forms of persistent channels, connecting the two sides of the heart, may result.

In one of the commonest varieties of malformed heart the *orifice of the pulmonary artery is much narrowed* and that of the aorta correspondingly enlarged, while the upper part of the interventricular septum (the last part to be developed) is absent. The aorta may subtend both ventricles, and the wall of the right ventricle will then attain the same thickness as that of the left. In these cases the ductus arteriosus is generally patent, and so, not infrequently, is the foramen ovale. In most instances, the narrowing of the pulmonary artery seems to be the primary defect, the rest naturally following from the interference with the normal course of the fœtal circulation ; for the blood from the right ventricle being unable to pass through the pulmonary orifice and ductus arteriosus into the systemic circulation, is driven over the upper edge of the incomplete septum and there meets that coming from the left ventricle, passing upward with it into the aorta. After birth the aorta supplies the pulmonary artery by way of the ductus arteriosus.

Stenosis or absence of the aortic orifice is less common. When either of these occurs, both foramen ovale and ductus arteriosus are usually patent, while the left ventricle atrophies.

The *valves* may be excessive or defective in number and in size, but these changes need not seriously interfere with the action of the heart.

Persistence of the foramen ovale and of the ductus arteriosus, although generally associated with the defects before mentioned, may occur alone, without leading to any further pathological change.

In the majority of cases the arrest of the normal development of the heart seems to depend primarily upon some inherent embryonic defect, and, only in exceptional cases, upon fœtal endocarditis or other intercurrent disease.

Results.—Malformations of the heart do not necessarily give rise to secondary changes, especially if limited to some slight defect, such as a patent foramen ovale or persistent ductus arteriosus, or some abnormality in the number of segments in a valve—none of which need cause any appreciable impairment of the circulation. If, however, the malformation is sufficiently severe to affect the normal order of the circulation without rendering life impossible, two phenomena generally occur: (1) *cyanosis*, constant or intermittent; and (2) a *high specific gravity of the blood*, due to an increased proportion of its red corpuscles.

(1) The *cyanosis* has been attributed to the admixture of arterial and venous blood; but this explanation appears inadequate. Admixture, as in the case of a single ventricle, may, however, exist without cyanosis; and, conversely, cyanosis without admixture. Moreover, it is in those cases in which the right ventricle is most hypertrophied that the cyanosis is most marked. With more reason, therefore, its presence is attributed to defective aëration of the blood and to passive (venous congestion). The deficient aëration may depend on structural alterations (stenosis of pulmonary artery with incomplete interventricular septum) whereby the amount of blood passing through the lungs varies. The aëration may be sufficient to meet the ordinary requirements, but insufficient to meet any slightly increased demands. In the same way the venous congestion is mainly due to the partial exhaustion of the normal reserve power of the heart, this having been already largely used up in compensating for the structural defects, and to the consequent inability of that organ to meet any further demand. Blueness of the skin and mucous membranes and clubbing of the fingers are the chief results of the venous congestion.

(2) The concentration of the blood, as shown in the large amount of red corpuscles and increased percentage of hæmoglobin, has been attributed to the persistence of a condition obtaining in late fœtal life, when the specific gravity of the blood is also abnormally high. Gibson suggests that the corpuscular excess is due to the diminished wear and tear, and the consequently longer life, of the individual corpuscles, but this view has not yet met with general acceptance.

Hypertrophy.

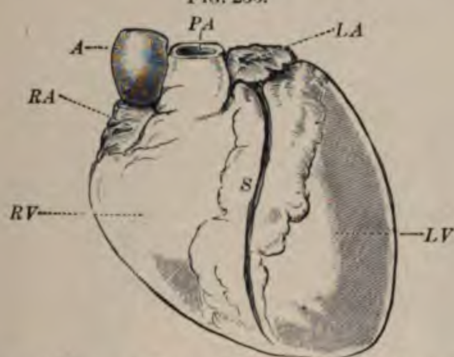
Hypertrophy of the heart has been already referred to (p. 85), but its varieties are of sufficient importance to merit a more detailed account. It must be recognized that hypertrophy of the heart is not in itself a disease, but that it takes place in response to altered conditions in the circulation, which the heart can only overcome by increased vigor of contraction. It is therefore of the nature of an attempt to remedy a defect elsewhere, and is beneficial, not the reverse. It is only pathological as being a departure from the normal condition.

The whole heart may be uniformly affected, or the enlargement may be mainly confined to one of the two ventricles.

Uniform hypertrophy of the whole organ is a common result of ent pericardium. By this change the sliding action of the heart rfered with, and the work thrown upon its muscular walls pro- nately increased. A heart thus enlarged may weigh from twelve ty ounces—even after the parietal layer of the pericardium has lissected off. The normal shape of the heart is preserved, but its l dimensions—both external and internal—and the thickness of lls are alike increased.

Hypertrophy of the left ventricle follows any changes that give

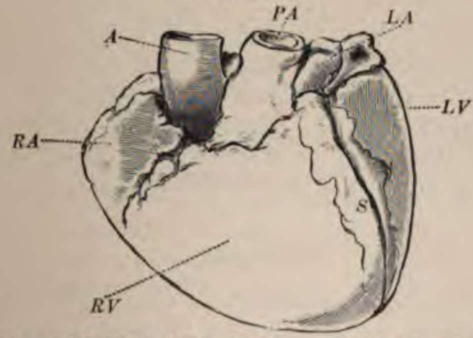
FIG. 255.



ophy of left ventricle (front view). Heart is elongated. Septum occupies middle of anterior surface. From a case of granular kidney.

obstruction at the aortic orifice, or permit regurgitation from the It also follows obstruction in the arterioles such as occurs in -capillary fibrosis (granular contracted kidney). The weight of

FIG. 256.



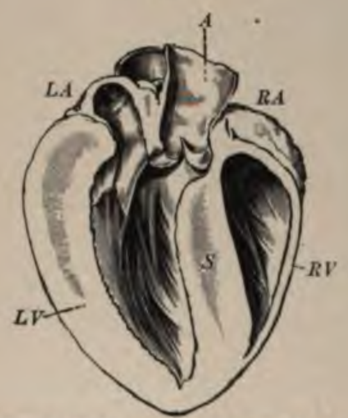
ophy of right ventricle (front view). Heart is quadrilateral and septum is displaced to left. Right auricle is dilated. From a case of chronic bronchitis and emphysema.

gan frequently exceeds twenty ounces. In shape it is elongated; ptum, and therefore the left coronary artery, is displaced to the of its usual position on the anterior surface (Fig. 255). On

examining a vertical section the apex is seen to be formed entirely by the wall of the left ventricle, and the walls of this cavity are themselves thickened (Fig. 257).

3. **Hypertrophy of the right ventricle** follows any changes in the mitral orifice, or in the lungs, which hinder the passage of the blood from the right ventricle to the systemic circulation and thus impose additional work on the right side of the heart. Emphysema of the lungs and incompetence of the mitral valves are its principal causes. The heart is quadrilateral, and its anterior surface consists, almost entirely, of the wall of the right ventricle (Fig. 256). On section, both ventricles

Fig. 257.



Anterior half of heart (Fig. 254) seen from behind. Left ventricle forms the whole of apex. Wall of *LV*; wall of *RV* : : 10 : 2 (normal proportion 5 : 2).

Fig. 258.

Anterior half of heart (Fig. 255) seen from behind. Right ventricle is seen to take greater share in formation of apex than left ventricle does. Wall of *RV* is much thickened, but not so thick as that of left. Tricuspid orifice and *RA* are dilated.

are found to take about an equal share in the formation of the apex of the organ, while the usual difference between the thickness of the walls is much diminished (Fig. 258). Except in cases of congenital disease, the thickness of the right ventricle never reaches that of the left. These distinctions are well shown in the accompanying illustrations.

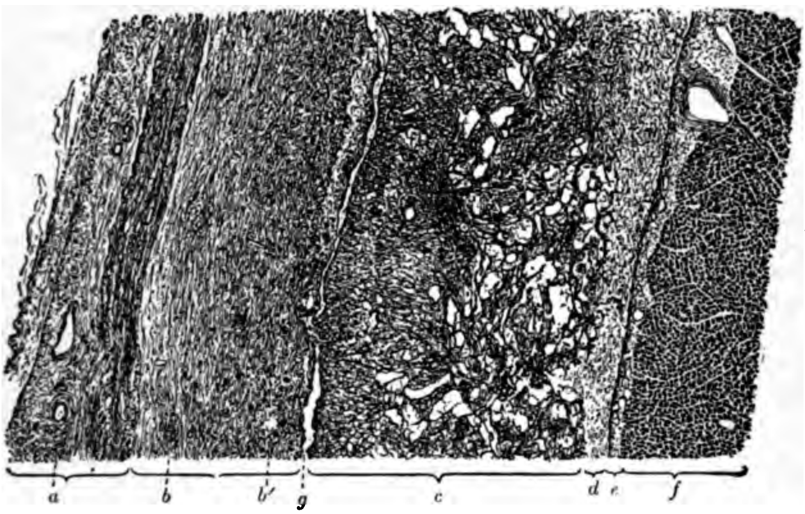
Pericarditis.

The irritant causing pericarditis—in most cases unknown—reaches the pericardium, as in inflammation of the other serous membranes, by way of the bloodvessels or by direct extension from the neighboring parts. In those cases in which organisms have been found associated with pericarditis they have been the same as those found in endocarditis—most commonly streptococci, pneumococci, and gonococci. In some cases, occurring in Bright's disease, no micro-organisms can

be found: it is possible that toxines alone may give rise to the inflammation in these instances.

The inflammatory exudation (p. 430) is accompanied by an exten-

FIG. 259.



Fibrinous pericarditis of two weeks' duration. *a*, parietal pericardium with artery and vein; *b*, organizing layer of fibrin, with engorged vessels appearing as dark points on its visceral edge (*b'*); *c*, fibrinous mesh work; *d*, organizing layer of fibrin adjoining visceral pericardium (*e*); *f*, muscular wall of heart with subpericardial fat and vessels; *g*, line of union of the two inflamed surfaces, showing that by far the larger amount of fibrinous exudation is on the visceral side. × 6.

sive destruction of the lining endothelium, and, in the vast majority of cases, is of a serofibrinous character. A fibrinous layer covers both visceral and parietal pericardium, and a few ounces of flaky albuminous fluid fill the intervening cavity. The fibrinous layer varies from a fine deposit, just concealing the natural gloss of the surface, to a layer ¼-inch thick, or a rough shaggy coat (*cor villosum*). The fluid effusion may in some cases reach a large amount, and considerably distend the pericardial sac: in some instances actual pus is formed.

The subsidence of the inflammation is followed by absorption of the fluid, and by organization of some, or all, of the fibrinous layers (Fig. 259). This results in obliteration of a proportionate amount of the pericardial cavity, or in the formation of fibrous bands passing across it.

During the acute stage the heart's action is slightly hampered (1) by the friction between the roughened surfaces, especially of the auricles and right ventricle; (2) by the pressure of any marked effusion of fluid; and (3) by the diminished support afforded by the weakened pericardium. There is also usually some extension of the inflammation to the outer layers of the myocardium. In the later stages the

action is also impaired by (1) the presence and contraction of such adhesions as have not been torn asunder, during the earlier stages of their development, by the movements of the muscular walls of the heart; and (2) by the contraction of the inflammatory fibrous tissue in the visceral pericardium and in the outer layers of the myocardium itself. The impairment is generally sufficient to cause uniform hypertrophy of the heart (p. 447).

On the surface of the pericardium smooth, white, "milk" patches are not infrequently observed. In a few cases these represent the most favorable termination of an old acute pericarditis; but the vast majority are most probably due to some source of pressure outside the pericardium, leading to considerable local friction between the visceral and parietal surfaces. At such places the pericardium becomes thickened and, therefore, whiter and more opaque.

Endocarditis.

Inflammation of the Endocardium, or *Endocarditis*, is, for the most part, limited to the *valves* of the heart, although it occasionally involves the adjacent parts. When the disease occurs *after birth* it is almost exclusively confined to the *left* side of the heart, and thus, in the great majority of cases, commences in, and seldom extends beyond, the confines of the mitral and of the aortic valves and the corresponding orifices; but when it arises during *fœtal life*, endocarditis is usually found on the *right* side and, by the production of lesions which interfere with the normal development of the heart, becomes one of the causes of congenital malformations of that organ.

FIG. 260.

Inflammation of mitral valve. The earlier stage of the process. Valve seen from the auricular surface. Showing the situation of the inflammatory granulations.

FIG. 261.

Inflammation of aortic valves. The earlier stage of the process. Showing the situation of the inflammatory granulations.

Those portions of the valves which normally come into contact, and are thus most exposed to friction, are those in which the morbid changes commence. In the *mitral valve*—the most commonly affected of all—the auricular surface of the segments, at a little distance from

the attachment of the chordæ tendinæ, is first involved (Fig. 260). In the *aortic* valves it is the convex or ventricular surface of the segments which is affected. The change does not commence at the free edge of the segment, but along the little band of tissue which passes from the attached border to the Corpus Arantii in the centre (Fig. 261).

The changes themselves may, for the purposes of description, be arranged in three groups, although they frequently occur together.

(1) Upon the surface of the parts already indicated are found a number of pale, closely aggregated projections, varying from a band of mere specks or beads, which cannot exert any appreciable mechanical effect on the heart's action (Fig. 261), to large cauliflower-like masses almost completely obstructing the affected orifice (Fig. 262). These projections, in the large majority of cases, consist of thickened endocardium and adherent, and often organized, blood-clots (Fig. 263). So smooth is the surface and so firm is the thrombus that, to superficial observation or until a section is made, these projections or vegetations appear to consist entirely of localized swellings of the endocardium. But when death occurs at a very early stage there may be no thickening of the endocardium at all, nor any redness—nothing but small

FIG. 262.

Endocarditis due to friction. The drawing represents a long vegetation on one of the segments of the aortic valve, which by contact with the endocardium below has produced numerous inflammatory granulations (A).

FIG. 263.

Acute endocarditis. A granulation from the mitral valve, showing a fibrinous coagulum upon the surface of the granulation (*d*). × 10. (Rindfleisch.)

areas of necrosed endocardium, each covered with a smooth, firmly adherent thrombus.

(2) The affected valves and their attachments may be much thickened throughout, and, at places, coherent and even calcified. In this way the mitral orifice may be reduced to a rigid funnel or buttonhole slit (Fig. 264), and the aortic valves may so lose there elasticity that they stand out into the lumen of the aorta, neither falling back during systole nor completely closing the orifice during diastole (Fig. 265). Thus the passage of blood through the orifices may be seriously inter-

FIG. 264.

Mitral stenosis. Mitral orifice seen from the left auricle in a case of old inflammation of the mitral valves. The orifice is in the centre of a calcified mass, the outer edge of which can be seen at *b*. A calcareous spicule projects into the orifice (*a*). Natural size.

FIG. 265.

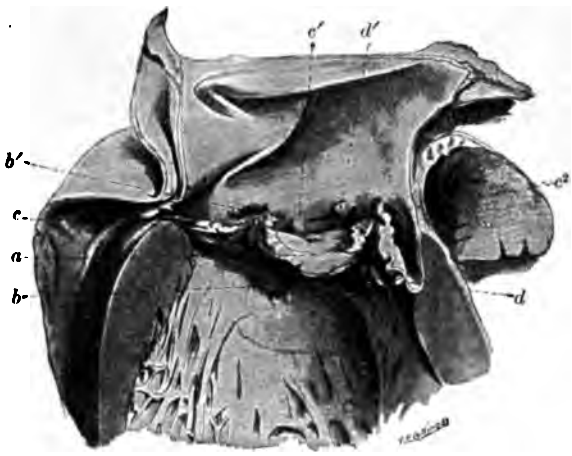
Aortic stenosis. *a*, aortic orifice seen from below in a case of old inflammation of the aortic valves. The valves are calcified and meet in the centre and at the sides; *b*, mitral valve (foreshortened). Natural size.

fered with (*stenosis*), and its regurgitation permitted (*incompetence*, pp. 85 and 203).

(3) Less frequently, and combined with the other changes, ulcers and minute abscesses may be found penetrating into the deeper layers of the endocardium and even involving the myocardium beneath. Portions of the valves may be wholly destroyed and disappear, while the superjacent and loosely adherent thrombi, being easily detached, broken up, and carried on by the circulating blood, may give rise to multiple embolism of the brain, spleen, kidney, skin, and other parts (Fig. 266).

Pathology.—The cause of endocarditis is an irritant circulating in the blood. In many cases this is known to be an organism. Organ-

FIG. 266.



Ulcerative endocarditis. *a*, adherent fibrinous masses concealing the attachments of the valves (*c*, *c'*, *c²*); *b*, *b'*, ulcers on endocardium and aorta; *d*, *d'*, inflammatory foci with adherent thrombi. Reduced ½.

isms have not only been found and cultivated from the lesions, but it has also been shown experimentally that the Staphylococcus pyogenes aureus, the Streptococcus pyogenes, the Diplococcus pneumoniæ, and the gonococcus are all capable, when injected into the circulation, of producing endocarditis. This probability is greatly increased when small solid particles are simultaneously introduced, or when the valves are in any way previously damaged. Other organisms, such as the Bacillus tuberculosis, are not found experimentally to produce endocarditis, unless some previous damage affords them a suitable resting-place. In a large number of cases the nature of the irritant is unknown. The disease frequently arises in the early stages of acute rheumatism and of chorea. It is an occasional complication of pyæmia, puerperal fever, gonorrhœal arthritis, scarlatina, typhoid fever, and chronic Bright's disease. The limitation of the disease, after birth, to the left side of the heart seems to be mainly due to the higher blood-pressure and greater friction, as well as to the greater oxygenation of

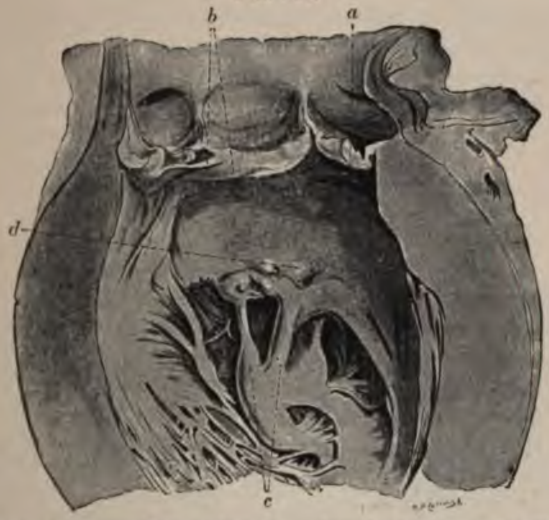
the blood which favors the growth of most of the organisms concerned. In fœtal life, on the other hand, the right side is more subject to strain than the left, and it is also more readily infected from the placenta.

The first effect of the irritant is to produce necrosis of the superficial layers of the endocardium. This is shown by the failure of the nuclei to stain. Upon these necrotic patches the passing blood coagulates in laminated thrombi. In many of the milder cases, according to some observers, no further change occurs, at any rate in the aortic valves, until reparative processes begin. According to others, multinuclear leucocytes appear in the neighborhood, and the endocardium swells. All agree that hyperæmia, visible to the naked eye, is rare, and that in the mitral valves, which are more freely supplied with vessels than the aortic, exudation occurs at an earlier stage.

The next stage varies with the irritant and with the treatment. (1) When the original invasion is slight and the necrosis superficial, and when the heart's action is as far as possible reduced, the proliferation of tissue-cells, characteristic of repair, quickly follows. Superficial parts of the firm and minute thrombi disappear and the remainder becomes organized (p. 217). The final result is a slight, permanent thickening of the affected parts with very slight narrowing or distortion of the orifice and its valves. (2) When the irritation is more intense or more prolonged, the necrosed patches are bigger and more numerous, while the adherent thrombi are proportionately larger. The term "warty" endocarditis is often applied to this form (*endocarditis verrucosa*) (Fig. 266). Distinct and considerable swelling of the endocardium follows, and the orifices may be partly blocked, and the valves rendered, to some extent, incompetent. Fragments of sufficient size to cause embolism may be detached from the thrombi, while pressure of the blood, *e. g.*, on the aortic valves during diastole, may produce a local bulging (*aneurism of valve*), or even a rent in that part of the valve where the necrosis of the endocardium on the opposite side has seriously weakened its resisting power. In these cases the reparative process is delayed, but when it does occur it is attended by much organization and, later on, in some cases, by calcification of the adherent thrombi and by the formation of much new cicatricial tissue in the valves and their attachments. In this way the extremest forms of distortion and rigidity, already alluded to, are produced. Sometimes there is but little evidence, either clinical or post-mortem, of any preceding acute disease. The changes are limited to thickening and rigidity of the orifices and their valves. It is possible that prolonged mechanical strain without any acute endocarditis may give rise to these changes, especially as œdema of the chordæ tendineæ has been observed, experimentally, to follow strain, and as the condition is often associated with chronic endarteritis, a disease also largely attributable to the same cause. Such changes are sometimes spoken of as *chronic endocarditis*, but the use of the term, if employed at all, should be limited to the reparative stage of the acute form (Fig. 267). (3) When the disease is due to an invasion of large numbers of

pyogenic bacteria, and especially when this affects a valve already the subject of a milder attack, the endocardium becomes the seat of miliary abscesses, and the *ulcerative*, *malignant*, or *infective* type of the

FIG. 267.



Old endocarditis—twenty years after acute attack. Aortic valves generally thickened (*a*), adherent (*b*), and somewhat rigid. Mitral valves thickened, adherent, and calcified; *c*, chordæ tendineæ thickened and shortened; calcified masses projecting through to the ventricular side of the valve. Orifice behind valve is reduced to a rigid buttonhole slit. Reduced ½.

disease occurs. The lesions in these cases are not confined to the valves, but readily spread to all parts which come into contact with them. Rupture of an aortic valve and aneurism of the heart, though never common accidents, occur more often in this than in other forms, but ulcers in the endocardium, and septic infarcts and miliary abscesses in distant parts, are both usual and characteristic.

Myocarditis.

Myocarditis, or inflammation of the cardiac walls, is less frequent than the preceding.

1. Suppurative inflammation occurs as a result of a pyæmic process. In these cases colonies of micro-organisms reach the muscular tissue either by way of the coronary arteries or by direct extension from an infective ulcer in the endocardium. Collections of leucocytes gather round them and the fibres in their neighborhood undergo necrosis. If the patient survive long enough, definite abscesses are formed. When the inflammation spreads through the wall of the heart to the endocardium, thrombosis may occur within the ventricle, owing to the injury to its lining membrance. This thrombosis is generally limited to the apical portion When the inflammatory foci are sufficiently numerous

the consequent weakening of the wall may give rise to aneurism: this is usually preceded by septic pericarditis.

2. A less intense form of myocarditis is met with in association with pericarditis and less commonly with endocarditis. Here the inflammatory process involves the immediately adjacent muscular layers of the organ which are found infiltrated with small cells, the fibres themselves being clear and structureless from coagulation-necrosis, or softened and granular from degeneration. A still more diffuse form of myocarditis, in which the heart is more generally involved, is found in certain cases of acute rheumatism, scarlatina, and other infective fevers. The microscopic appearances are much the same as those just described. Leucocytes is varying numbers infiltrate the intermuscular tissue, which may also be the seat of minute hemorrhages. The change is most marked in the left ventricle, and is also usually associated with endocarditis or pericarditis (Fig. 268).

FIG. 268.

Acute rheumatic myocarditis, associated with endo- and pericarditis. To the naked eye, the myocardium was "fatty" only. The tissues around the artery, seen in longitudinal section, are infiltrated with leucocytes, and hemorrhage has occurred on the right-hand side. Above this point the fibres are granular. A case of myocarditis ending in sudden death. (Mott.)

Myomalacia Cordis.

1. *Myomalacia cordis* is the term applied by Ziegler to the occurrence of necrosed areas in the myocardium as a result of the local deprivation of arterial blood. Usually this is due to thrombosis of some branch, large or small, of an atheromatous or otherwise diseased coronary artery. Occasionally it may be due to embolism. The left ventricle is more commonly affected than the right, and the apex more often

ny other part. If the necrosed areas be large or numerous, and l to the endocardium, aneurysm of the heart and thrombosis in the of the left ventricle (apex) may follow (Fig. 269).

tissues supplied by the blocked vessel generally undergo coagula-ecrosis, in which process even the connective-tissue cells may occa-ly participate. As a rule, however, in the areas where the muscle-

FIG. 269.

m of the heart, with thrombosis in the cavity of the left ventricle, and commencing carditis—from a case of myomalacia cordis. *a*, laminated thrombus with softened centre pying the aneurismal pouch in the ventricular walls; *b*, extension of laminated throm- adherent to the septum in the direction of the aorta; *c*, incision to show nature of mbus; *d*, fibrinous exudation on inflamed pericardium; *e*, *e'*, wall of aneurism formed nyocardium; *f*, wall of aneurism formed by pericardium. Reduced 1/3.

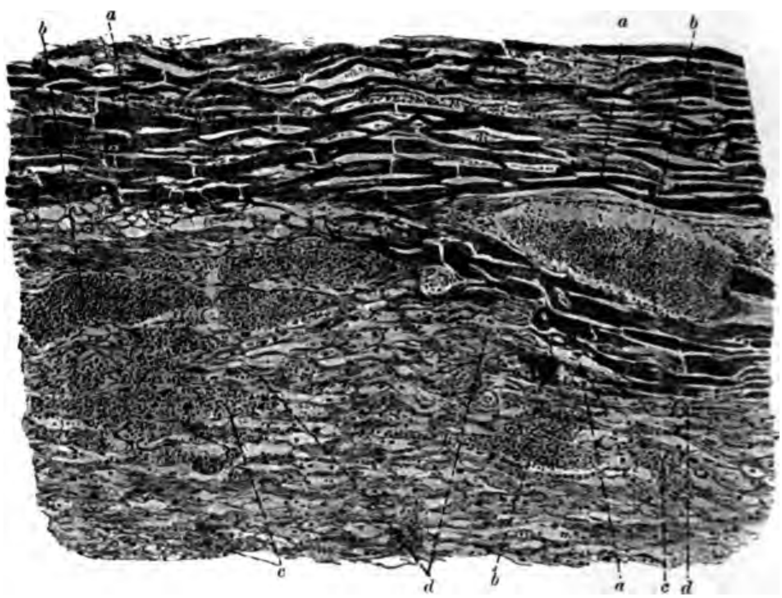
have disappeared the connective-tissue nuclei still stain readily 270). Sometimes the necrosed areas are infiltrated with blood the neighboring capillaries (infarction). If the hemorrhage be s, the color, to the naked eye, will be dark red. If no hemor- occur, it will be yellow; if the hemorrhage be only small in t, the affected portion may have a red border and a yellow centre, of a mottled tint, according to the extent of the extravasation. y case, the older the lesion the grayer its color. This change in

color is due to the reparative processes which follow. The necrosed areas soon become penetrated, and replaced by young fibrous tissue, and, later on, are converted into hard cicatricial masses. When a number of such areas have been thus replaced by scar-tissue, the term *fibroid heart* is applied to the affected organ.

Fibroid Heart.

According to some authorities, *myomalacia cordis* is the most frequent cause of a fibroid heart, but many of the cases of the latter disease may be probably attributed to (1) the reparative process following a gradual atrophy of the fibres, dependent on endarteritis of the smaller

FIG. 270.



A necrosed patch in the myocardium. At *d*, where the muscle-fibres have disappeared, the structure consists of the connective-tissue stroma and the débris of necrosed muscle-fibres. At other places engorged bloodvessels and extravasated blood (*b*, *c*) are seen. The muscle-fibres remaining (*a*) have lost their striation. × 150.

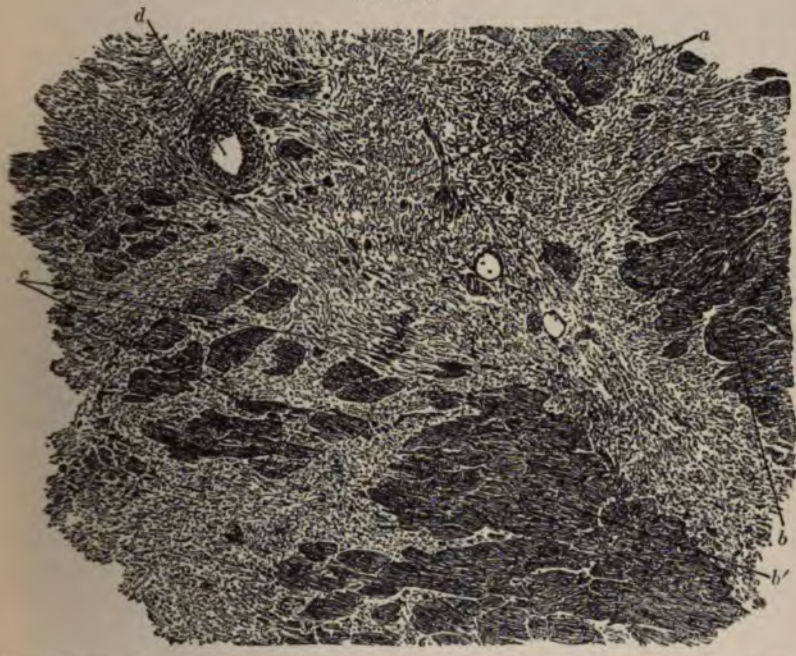
vessels, and on the consequent gradual diminution of the blood-supply; (2) to a similar reparative process succeeding the myocarditis occurring in some of the infective fevers; (3) to prolonged venous engorgement of the heart; (4) to the final stage of syphilitic gummata; and (5) to pericarditis. When secondary to pericarditis, the change is usually most advanced in the more external portions of the cardiac walls, and commonly affects both the right and left ventricles.

Whatever the cause, the heart is usually enlarged, and fatty degeneration of the muscular fibres is found outside the fibroid areas. More-

over, the function of the heart is materially impaired, and fibroid induration accordingly constitutes one of the gravest of all cardiac diseases (Fig. 271).

Effects of Cardiac Disease.—The effect of almost every lesion of the heart, whether of the myocardium or of the valves, is to diminish the driving-power of the organ and thus to impair the circulation of the blood. The general result is to render the patient short of breath on exertion, owing to lack of reserve power. If the valves are diseased, compensation may at first be effected by hypertrophy and

FIG. 271.



Fibroid heart. Showing broad strands of cicatricial tissue (*a*) between groups of muscle-fibres (*b*, *b′*), many of which are entirely separated from each other (*c*); *d*, oblique section through an artery. In a similar section from a normal heart nearly the whole area would be occupied by the muscle-fibres. × 75. (From a specimen by Dr. Rolleston.)

increased work of the heart; and no further symptoms may be apparent. If compensation fails, either owing to myocardial disease, or to some obstruction to the flow of blood, or to increased exertion, disorder of the circulation ensues. If the *mitral valve* be affected the blood tends to collect in the pulmonary veins; the pressure in the bloodvessels within the lungs is raised; and more work is thrown upon the right ventricle, which has to contract more vigorously to overcome the pressure in front of it. If it in turn fail, engorgement of the systemic veins ensues, with resulting cyanosis and œdema. The results of venous engorgement upon the various organs of the body are described else-

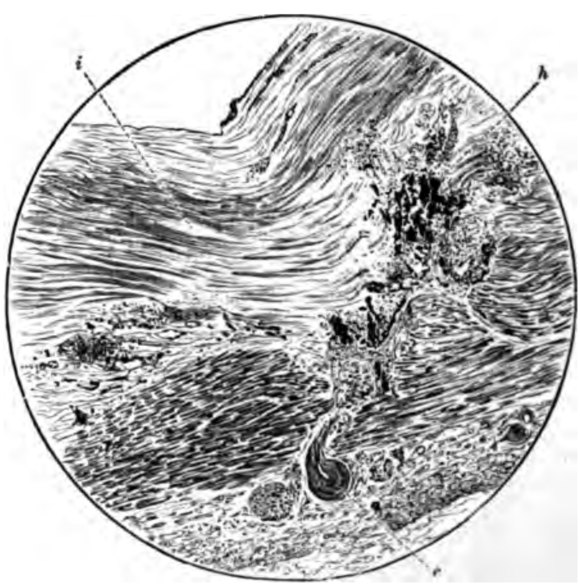
where (see pp. 198–204), and the causation of cardiac dropsy is also considered in Chap. VII. If the *aortic valves* be the seat of disease, and failure of compensation occur, the arteries are insufficiently filled with blood and the nutrition of the body suffers. Cerebral anæmia may result in attacks of syncope. The dilatation of the left ventricle which occurs in aortic disease may finally be so great as to cause relative incompetence of the mitral valves through stretching of this orifice, and symptoms of mitral failure will be superadded to the aortic. Severe cardiac pain (*angina pectoris*) often accompanies aortic disease and is called out by any sudden rise of blood-pressure in the arterial system.

Failure of the heart is generally accompanied by frequency, and often by irregularity, of its action; but in some cases, especially in myocardial disease, an unduly infrequent pulse may be encountered.

VII. DISEASES OF BLOODVESSELS.

It is generally taught that the middle and inner coats of arteries are non-vascular, the *vasa vasorum* not penetrating beyond the external

FIG. 272.



Section of an atheromatous aorta : the intima is much thickened (*i*) ; passing in from the externa through the media are vessels, about which hemorrhage (*h*) has occurred ; the lumina of the main trunks of these (*e*) in the externa are almost obliterated by an endarteritis. (Mott.)

coat ; and that the intima is nourished by the blood in the lumen of the vessel. But Mott has shown that the vasa vasorum may enter the media, even in normal arteries, and has suggested that the apertures in the membrana fenestrata may allow fluids to pass from the vasa

vasorum into the intima. In support of the view that the intima is not nourished solely by the blood within the lumen of the vessel, Mott has shown that it may persist around thrombi, which must have cut off that source of supply (Fig. 111).

Moreover, the proliferative arteries which occurs in the organization of thrombi affords additional support to this conclusion (p. 217), It is quite certain that, in chronic inflammation of the arteries, vasa vasorum frequently penetrate into the middle, and even the inner, coat (Fig. 272).

Degenerative Changes in Arteries.

The walls of arteries are liable to various forms of degeneration. *Fatty degeneration* may affect the intima or the media (p. 60); *hyaline degeneration* is generally limited to the intima (p. 65); while *amyloid disease*, though commencing in the intima, frequently involves all three coats (p. 66). *Calcification* is generally secondary to one or other of the foregoing degenerations (p. 78).

Inflammation of Arteries.

(1) *Infective Arteritis.*—In this disease, pyogenic cocci are conveyed to the wall of an artery, either by its vasa vasorum or by the blood within its lumen, and there give rise to an *abscess*. In most cases this is found in the media, or between the media and the adventitia. The wall is softened and infiltrated with leucocytes, and, in places, all trace of its original structure may be lost. Thrombosis, dilatation of the lumen (*aneurism*), and rupture of the vessel are common results of this condition.

An acute form of arteritis, known as *periarteritis nodosa*, is described. It may affect all arteries except the pulmonary, and is characterized by the presence of nodules on the outside of the vessels, representing inflammatory foci and involving the adventitia and media. Such cases are probably of infective origin: many are attributable to syphilis, a similar condition being found in gummata.

(2) *Proliferative Arteritis.*—Thickening of the intima and media, by proliferation of their component cells, is sometimes met with. It is accompanied by diminution of the lumen of the vessel, and occasionally by complete obliteration (p. 216). This condition frequently follows torsion, ligature and other injuries, embolism, and thrombosis. The cause, whether it be some irritant conveyed by the vasa vasorum, or some kind of mechanical damage, is, in most cases, non-infective; but micro-organisms are occasionally met with, presumably of a low degree of virulence.

(3) *Aortitis.*—A special form of arteritis is described in connection with the aorta. It leads to the formation of small, pearly, pinkish patches slightly raised above the surface of the intima. These are mainly due to a proliferation of the cells of the part: parietal thrombi

may be deposited on their surface. In many cases the condition appears to be due to syphilis.

Arteriosclerosis.

This term includes all chronic degenerative changes peculiar to arteries, other than those immediately due to syphilis.

Two forms are generally described, the *nodular* and the *diffuse*.

(1) The **nodular** form, often known as *atheroma*, affects chiefly the larger vessels and those at the base of the brain. In its early stages it

FIG. 273.

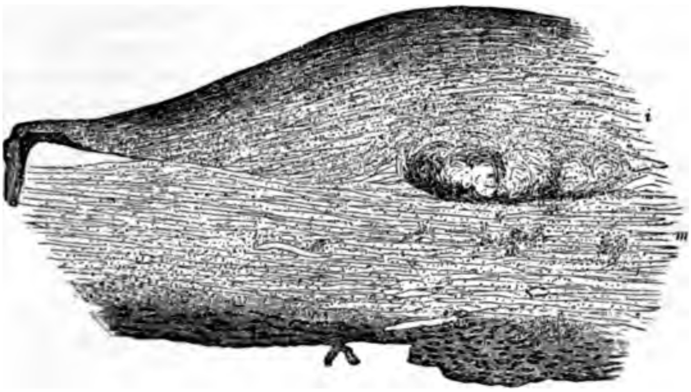
Obliterative arteritis of internal carotid. × 12. (From a specimen by Dr. Rolleston.)

takes the form of gelatinous, slightly raised, yellowish patches, covered by endothelium. In cases of long standing, firm, fibrous, or calcified plates, covered with endothelium or exposed to the blood-stream, may be present. The circumference of the lumen is not uniformly affected (Fig. 273), although complete rings may be found round the mouths of branches where they leave the main trunk. The arch of the aorta, a common seat of the change, is often so studded with small, thickly set, raised plaques, that it resembles crocodile-skin. Sometimes the patches of new tissue may undergo fatty degeneration, and subsequently softening. In the latter case, soft, yellowish, pultaceous material, consisting of fatty débris and cholesterin crystals, is found in the deeper layers of the intima. This has been termed an *atheromatous abscess*. If the superficial layers of the intima degenerate or are torn,

the degenerated products may be discharged into the blood-stream and an *atheromatous ulcer* be left.

The orifices and branches of the coronary arteries are particularly

FIG. 274.



Arteriosclerosis (atheroma) of the aorta. Showing the localized thickening of the inner coat and the apparent bulging inward of the vessel. Some of the new tissue has undergone fatty degeneration. There is also some thickening of the middle coat. *i*, internal; *m*, middle; *e*, external coat of vessel. × 25.

liable to atheromatous changes, and are often much narrowed. The blood-supply of the heart is, in these cases, proportionately lessened, and the tendency to fatty degeneration of its muscular walls increased. It is by no means certain that the patches, which project into the lumen after death (Fig. 274), do so during life; for Thoma found that if atheromatous arteries were injected with melted paraffine, at a pressure equal to that of the blood-stream, the solid casts obtained were cylindrical and showed no corresponding depressions.

Under the microscope, in the earliest stages of the process, the deeper layers of the intima are found to be much thickened. The thickening is probably due to a proliferation of the component cells, and the proliferation may possibly be the result of the action of bacterial products or of some other irritant. Many of the new cells may develop into fibrous tissue, resulting in a dense fibroid plaque or in a more diffuse thickening. Areas of fatty degeneration are generally found in the central and deepest parts of these patches of fibrous tissue. The muscle-fibres of the middle coat become swollen and undergo hyaline degeneration, while the elastic tissue atrophies, its fibres being sometimes ruptured.

(2) The **diffuse** form affects smaller arteries and causes great thickening of their walls, with a marked, if not proportionate, diminution of their lumina. The changes are more uniformly distributed than in the nodular form of the disease. Both the intima and media undergo hyaline degeneration, and the internal elastic lamina in many places disappears. This condition corresponds to the *arteriocapillary fibrosis* of Gull and Sutton, and is found associated with hypertrophy and fibrosis

of the heart and atrophy of the kidneys (*granular contracted kidney*)—the commonest form of chronic Bright's disease.

Results.—It is obvious that the changes which have been described will gradually impair the strength and elasticity of the vessel-walls, and thus affect the circulation in the parts beyond. Moreover, the diminution of the lumen, and the change in the lining membrane of the vessel, will predispose to thrombosis and occasionally give rise to embolism. On rare occasions the narrowing of the vessel may be so great as practically to obliterate the lumen and to produce gangrene of the parts supplied. This condition is often spoken of as *obliterative arteritis*, and is by some regarded as a distinct disease. The loss of strength in the vessel-wall will cause it to give way under the constant pressure—**aneurism.** General dilatation of the vessel may result: when this is extreme, it is known as a *fusiform* aneurism. When the vessel is especially weakened at one spot—for instance, by the formation of an atheromatous ulcer or by the rupture of its middle coat—a local dilatation or *sacculated* aneurism may occur (Fig. 275). When this has reached a certain size, its wall may rupture, and fatal hemorrhage result. If the external coats have been uniformly strengthened by the formation of chronic inflammatory tissue in them, this result will be proportionately delayed. If an atheromatous abscess bursts before the tissues round its margin have been matted together by fibroid growth, the blood may find its way into the substance of the *media*, and, making for itself a cavity between the coats of the vessel, form a *dissecting* aneurism. This occurs only in the aorta and its largest branches. Ultimately the blood may burst either through the *externa* into the surrounding tissues, or through the *intima* into the lumen of the vessel.

FIG. 275.

Miliary aneurisms on a branch of the middle cerebral artery, from a case of cerebral hemorrhage. They are not unlike birds' nests in a tree. (Mott.)

The affected parts show the usual results of impaired blood-supply (pp. 42, 51, 181).

Etiology.—Arteriosclerosis must unquestionably be classed amongst *senile* changes. Like other senile manifestations, it occurs much earlier in some persons than in others. It is highly probable that it is also *hereditary*, a belief mainly based upon the early occurrence of arterial degeneration in those whose ancestors have succumbed to apoplexy. Its advent is also accelerated by the presence of gout, alcoholism, plumbism, spphilis, mechanical strain, and any cause which increases the blood-pressure. *Gout* is associated with the presence of toxic bodies, while alcohol and lead probably exert a direct poisonous action upon the vessel. *Syphilis*, in addition to the equally pernicious influence of its assumed toxin, causes endarteritis of the vasa vasorum (Mott) (Fig. 276). The proofs that *mechanical strain* has a special influence in its production are: (1) the much greater frequency of arteriosclerosis in

the aortic than in the pulmonary system ; (2) its occurrence in the latter when its blood-pressure is raised, as in mitral obstruction ; (3) its relative frequency in those systemic arteries which are most exposed to strain, especially the arch of the aorta ; and (4) its presence in conditions accompanied by rise of blood-pressure. Athletes, and those engaged in laborious occupations, are especially liable to the disease.

Pathology.—There is no generally accepted explanation of the processes which culminate in advanced arteriosclerosis. Thoma, whose work on this subject is very exhaustive, believes that loss of elasticity in the arterial walls is the primary change. This is followed by distention of the affected vessel and slowing of the blood-stream. Compensatory thickening of the intima follows, tending to reduce the

FIG. 276.

External coat of aorta in an early stage of arteriosclerosis, showing peri-arteritis and cell-infiltration from the vasa vasorum. The walls of the vasa vasorum seen in section are much thickened. It was a markedly syphilitic case. × 110. (Mott.)

calibre of the dilated vessels to its original size, and so maintain the normal rate of blood-stream. Unfortunately the nutrition of the new tissue cannot, in most cases, be maintained—hence degeneration of the thickened intima follows. Thoma found that the local patches of thickened intima exactly correspond to the places where the media was giving way, and obtained additional evidence in favor of his view by the injection of the bloodvessels already referred to (p. 463). In Thoma's opinion, the thickening of the intima is a conservative process.

By these changes the vessel is converted into a more or less rigid tube, and the circulation is proportionately impaired. This difficulty is overcome by the increased action and hypertrophy of the left ventricle of the heart. But this hypothesis does not explain why primary

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weakening occurs. Mott's view, that this is due to an endarteritis of the vasa vasorum, which is frequently present, is in many cases highly probable (Fig. 262); but the cause of this endarteritis has then to be elucidated. It is not improbable that the toxines of infective disease produce the primary injury to the arterial walls in some instances, either acting on the middle coat directly or on the vasa vasorum. In other cases the loss of elasticity may be a true senile change, as it often seems to be in emphysema.

Inflammation of Veins.

Inflammation of veins (*phlebitis*) is very analogous to inflammation of arteries. *Acute infective phlebitis* is decidedly more frequent than acute infective arteritis. In most cases it is due to the presence and growth of organisms (*acute suppurative phlebitis*). The wall of the vein becomes swollen and densely infiltrated with multinucleated leucocytes. All appearance of normal structure is lost, the cells nearest the lumen die and are cast off, as in the wall of an abscess, into which the wall of the vein has been practically converted (Fig. 277). Septic thrombosis follows and, in many cases, pyæmia.

FIG. 277.

Section through a portal canal in a case of suppurative pylephlebitis arising in connection with "umbilical pyæmia." The vein-wall (V) is converted into granulation-tissue. Lumen of vein is below on the left. × 60. (Boyd.)

Non-infective and *proliferative phlebitis* are due to the same causes, and present the same appearances, as the similar affections of arteries. A recurrent phlebitis, especially common in the internal saphenous vein, is frequently met with in gout.

A *phlebosclerosis*, somewhat similar to arteriosclerosis, may be found in the pulmonary veins in cases of mitral stenosis, and in the portal veins in cirrhosis of the liver, as well as combined with arteriosclerosis, and due to the same causes.

Varicose Veins.

In some persons especially predisposed, constant but comparatively slight increase of the pressure in the veins of the legs, spermatic cord, or rectum, will produce an irregular but very marked dilatation, lengthening, and tortuosity of the vessels in question. Portal obstruction will produce the same results in the veins of the hemorrhoidal plexus apparently *without* any predisposition. Other veins are similarly, but less frequently, affected. The dilatation and other changes may be accompanied by thickening of the walls, due to the formation of fibrous tissue.

When the dilatation is mainly saccular in form, the walls may be exceedingly thin and easily rupture: this is frequently the case when the rectal veins are involved (*hemorrhoids*). The projecting skin or mucous membrane covering varicose veins is especially liable to friction. The excoriation thus produced is followed by progressive ulceration, which only heals when the increased venous pressure is removed. When the friction is less severe, overgrowth of the surrounding connective tissue may occur. Thrombi and phleboliths may be found within the dilated veins. In some instances varicose veins may perhaps be angiomatous in nature.

VIII. DISEASES OF THE RESPIRATORY ORGANS.

Pneumonia.

In the lungs, inflammatory processes may, for convenience of description, be divided into three varieties: (1) *croupous*, lobar, or acute pneumonia; (2) *catarrhal*, lobular, or bronchopneumonia; and (3) *interstitial*, or chronic pneumonia.

1. Acute, Croupous, or Lobar Pneumonia.

Acute pneumonia is an infective disease characterized by inflammation of the lung, leading to the solidification of a considerable area of the organ. It is usually limited to one lung, and the right is most frequently affected. The inflammation starts in the substance of the lung, from a focus which, in the majority of cases, is in the lower part of the lower lobe. The disease extends by continuity of tissue from this primary focus. The consolidated portion may exactly correspond to a single lobe, though quite as often it is less or more than this.

The inflammation of the lung is always accompanied by inflamma-

tion of the pleura over the inflamed area, and sometimes, owing to the spread of the infection, by that of the peritoneum and pericardium. The bronchial glands are inflamed and swollen, the mediastinal connective tissue is frequently œdematous, and acute secondary meningitis occasionally supervenes. The disease is accompanied by a high temperature, beginning with a sudden rise (p. 230), and ending by crisis; cloudy swelling of organs results. Death, when it occurs, seems to be due to cardiac failure, induced by general poisoning.

Etiology.—This disease was formerly attributed to a chill, and, in certain cases, its connection with exposure to cold and damp is very striking. Exposure is, however, only a predisposing cause, for it occurs in but a small minority of the cases. Moreover, although the disease is most prevalent in the early spring, it does not especially affect those who are most exposed to the vicissitudes of the weather, nor does its prevalence rise and fall with that of bronchitis.

Similarly, depressed health is only a predisposing cause. Typically healthy people are often affected, but it is especially liable to occur as a complication in cases of erysipelas, typhoid fever, chronic alcoholism, and other debilitating diseases. Pneumonia is prone to recur in a person who has once suffered from it.

The disease is occasionally so prevalent as to be practically epidemic. Small outbreaks occasionally occur in wards, prisons, and similar places; the disease is sometimes endemic in a house, from time to time attacking different people in it; but there is in general no evidence that it is contagious.

Pathology.—Acute pneumonia is a general infective disease in which the inflammation of the lung is the characteristic local lesion. This is shown by the typical course of the fever, ending usually in a crisis between the fifth and eighth days, and by the absence of any constant relationship between the extent of the local inflammation and the intensity of the fever. The gravity of the disease is proportional to the intensity of the toxines at work, the actual interference with the respiratory function being only of secondary importance. Death occurs by cardiac failure resulting from the toxæmia, not by deficient aëration of the blood.

In the large majority of cases the disease is due to the growth of the Diplococcus pneumoniæ (p. 311). Less commonly Friedländer's bacillus, streptococci, or the bacilli of tuberculosis, typhoid fever, or diphtheria have been found, especially in pneumonia occurring in the course of other diseases. But even in these secondary pneumonias the

FIG. 278.—Acute lobar pneumonia (red hepatization). Vertical section through left lung. *A, B,* advancing margin of pneumonic area, with hyperæmic edges; *C*, hemorrhagic area; *D*, fissure between upper and lower lobes; *E*, normal lung; *F*, larger bronchi; *G*, bronchial glands with pigment; *H*, consolidated area; *I, I'*, pulmonary vein; *K*, engorged area, showing commencement of pneumonic process. Between *K* and *B* several of these areas may be seen. In this specimen, *contrary to the usual rule*, the pneumonia commenced in the upper lobe and spread downward, death ensuing on the fifth day. $\times \frac{3}{4}$.

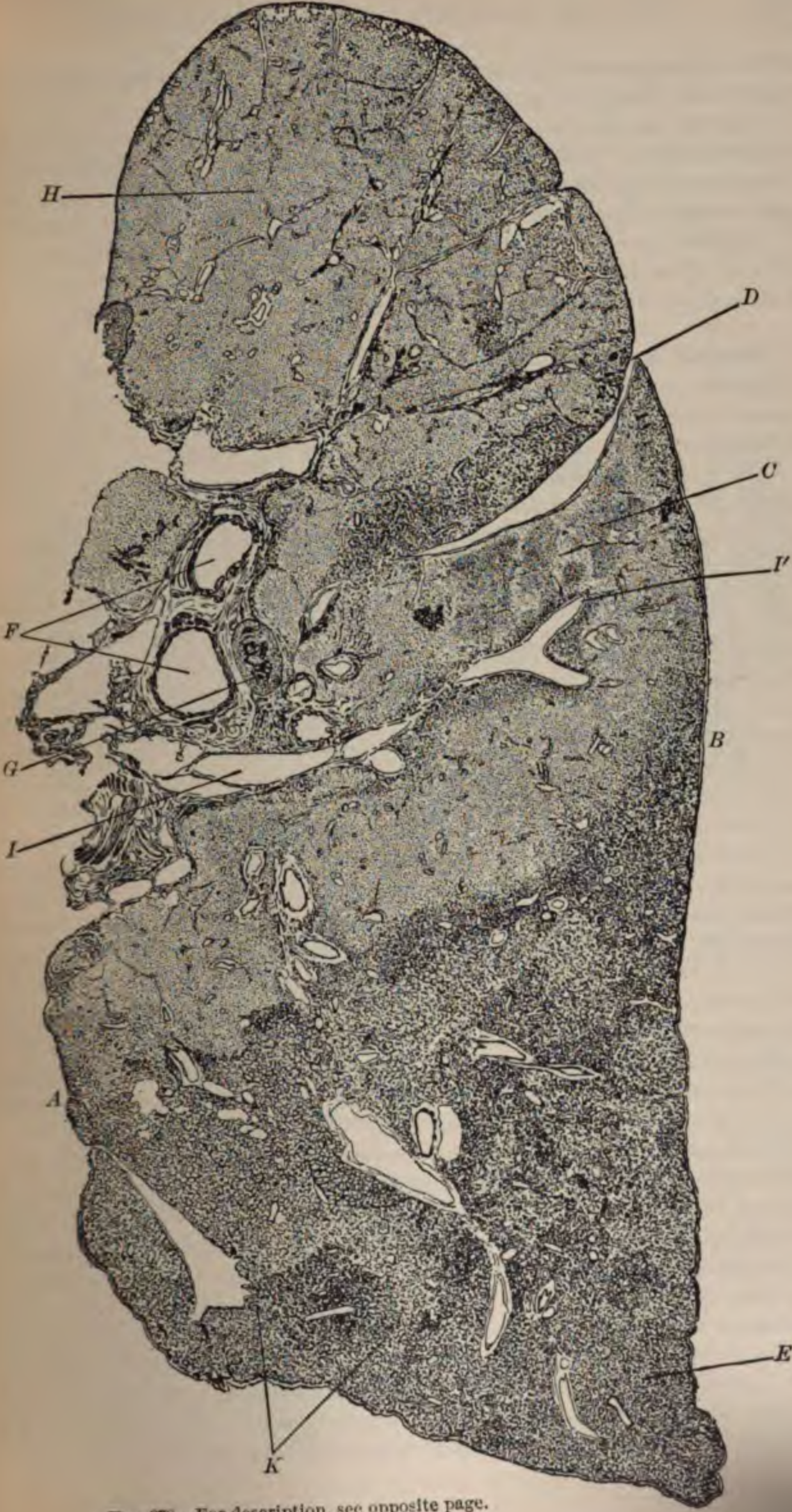


FIG. 278.—For description, see opposite page.

Diplococcus pneumoniæ (pneumococcus) is the organism most frequently met with. The precise method of infection is unknown.

The pneumococcus exists normally in the mouth, and can generally be found on the surface of the tonsils. Indeed, all the organisms just mentioned may be met with in the air-passages of persons free from pneumonia. Experimentally, any of these organisms may be blown into the trachea without causing this disease; but pneumonia follows (1) if dust be simultaneously injected; or (2) if the animals, after being kept warm, are suddenly immersed in a cold bath at the time of the injection.

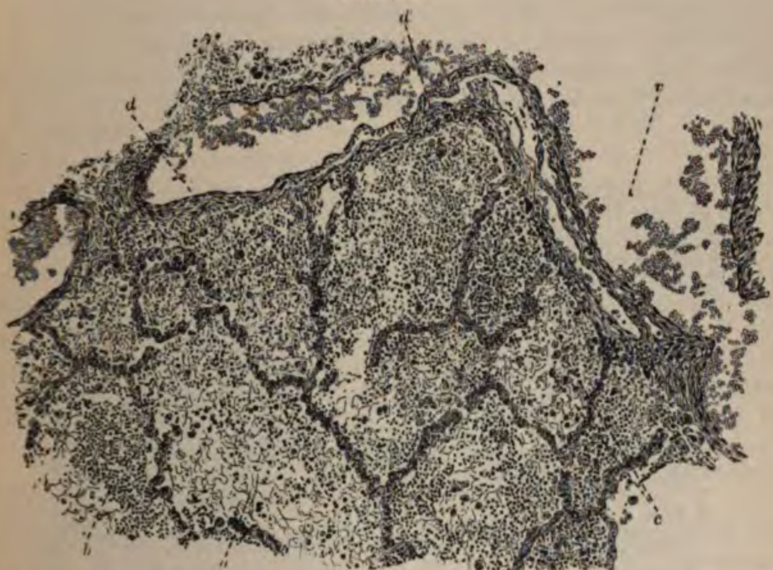
Morbid Anatomy.—The local process is characterized by intense inflammatory hyperæmia of the lung, and by the exudation of a large amount of coagulable material into the pulmonary tissue. It is termed "croupous" from the fibrinous character of the exudation. The term "lobar" is applied to it because it almost invariably affects an extensive portion of the lung. The process is commonly described as consisting of three stages—(1) that of *engorgement;* (2) that of *red hepatization;* and (3) that of *gray hepatization.*

In the *first* stage, that of **engorgement,** small patches of lung-tissue, only visible in large, thin sections, become intensely hyperæmic and rapidly run together to form a large uniformly engorged dark-red area. The weight of this congested portion of the lung is increased, its elasticity is diminished, its substance is less crepitant and more friable than natural, and its surface pits upon pressure. On section, it yields a reddish, frothy, tenacious liquid.

In the *second* stage, that of **red hepatization,** there is an exudation of fluid and blood-corpuscles into the pulmonary tissue. Some of the vessels may also rupture and small extravasations occur. The exuded liquids coagulate within the air-vesicles and terminal bronchioles, and form a semi-transparent coagulum enclosing red corpuscles and leucocytes in its meshes (Fig. 279). The fibrin-filaments, according to Weichselbaum, are much thicker and more numerous in cases due to the Diplococcus pneumoniæ. Contrary to the usual rule in acute inflammations, the uninucleated leucocytes are as plentiful as the multinucleated: both forms may contain pneumococci. The lung is now much heavier than in the preceding stage, and is increased in size, so as to be often marked by the ribs. The affected portion can be recognized before a section is made, for the pleura over it is hyperæmic, opaque, and covered with fibrinous exudation, while the distention, firmness, and dark purple color of the lung beneath cannot escape notice. It is quite solid, sinks in water, and cannot be artificially inflated. It does not crepitate under the fingers, and is remarkably friable, breaking down readily with a soft granular fracture. The cut surface has a granular appearance, seen especially when the tissue is torn. This is owing to the small masses of coagulated exudation, which project from the alveoli they fill. There is no lobulation of the margin of the inflamed area, no outlying racemose nodules or other indication of infection spreading by the bronchi. The color is of a dark reddish-brown, here and there passing into gray.

This admixture with gray sometimes gives a marbled appearance. The red color is due chiefly to vascular engorgement, but partly to extravasated red corpuscles. Throughout this stage the vessels in the alveolar walls are engorged, while the alveolar epithelium is usually swollen and granular. If a section of the spreading edge be examined at this stage, it will be found intensely hyperæmic. The hyperæmia extends irregularly into the adjacent tissue (Fig. 278).

FIG. 279.



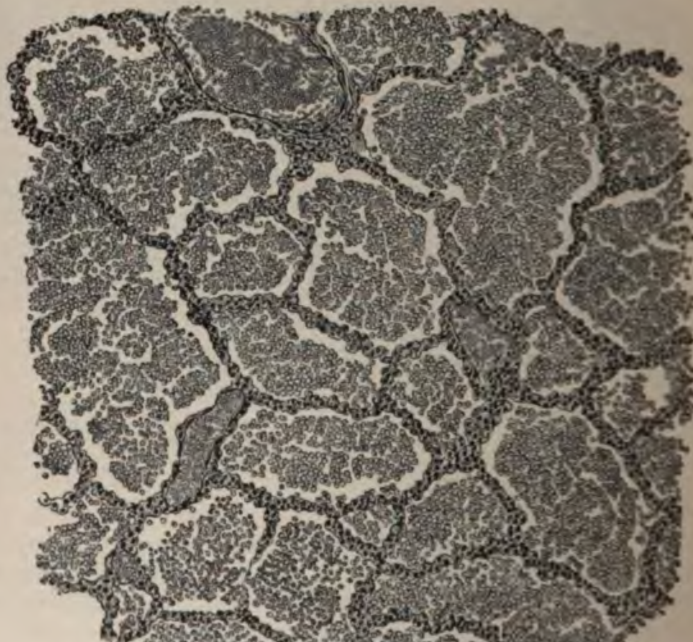
Acute lobar pneumonia (red hepatization). *a*, alveolus containing fibrin-filaments and a few blood-corpuscles; *b*, alveolus containing a larger proportion of corpuscles; *c* and *d*, desquamated alveolar epithelium; *v*, vein. Most of the red blood-corpuscles in the alveoli are stained; those in the vein are unstained. × 120.

The *third* stage, that of **gray hepatization,** is characterized by a marked emigration of leucocytes, and by more extensive degenerative changes in the alveolar epithelium. The walls of the alveoli are infiltrated, and their cavities distended with the emigrated leucocytes. The walls and the contents of the alveoli now assume a uniform appearance, and the granular appearance of the red stage is lost (Fig. 279). The fibrinous material next disintegrates, and the white cells rapidly undergo fatty changes, whilst the red are decolorized, so that the alveoli are seen to be full of granular elements, which in many parts have lost their distinctive outlines (Fig. 280). Occasionally, when this stage is unusually advanced, the alveolar walls may be found, here and there, partially destroyed. The weight, density, and friability of the lung are now even greater than in the stage of red hepatization. The tissue is soft and pulpy, and a puriform liquid exudes from its cut surface. The most prominent feature, however, is the difference in the color of the organ. Instead of

a dark, redish-brown color, the section now appears a gray or yellowish-white, marbled by the tracts of pigment-bearing connective tissue. The pallor is owing partly to the fatty degeneration which the cells have undergone, and partly to the pressure exercised upon the bloodvessels by the exuded substances and newly formed cells; but since Rindfleisch has shown that it is always easy to inject the vessels, it would seem likely that a good deal of the pallor is due to the fall in blood-pressure after death. The stage of gray hepatization, when far advanced, has been termed "suppuration, or purulent infiltration, of the lung." This, in all probability, only occurs in fatal cases.

Although these three stages of the pneumonic process have been described as succeeding one another in orderly succession, it must be remembered not only that each stage does not occur simultaneously

Fig. 280.



Acute lobar pneumonia (gray hepatization). Lobules full of degenerating leucocytes and fluid exudation; and two veins full of red blood-corpuscles. × 100.

throughout the whole of the affected area of the lung, but that in some cases it is more accurate to speak of only two stages—*engorgement* and *hepatization*. Patches of gray hepatization may be found in recently invaded parts of the lung, and patches of red hepatization in those portions which were earliest affected. The exact characters of these changes not improbably depend on the presence of centres of infection, on the nature and virulence of the organisms present, and on the local conditions influencing their growth. According to this explanation, the exudation first filling the alveoli remains unaltered until degeneration

and disintegration set in. The bronchi in the affected area are always inflamed, and usually contain a viscid, blood-stained, rust-colored mucus, which forms the characteristic expectoration. Sometimes the sputum is dark and watery, like prune-juice. This is probably owing to the addition of serous exudation from neighboring parts of the lung.

Terminations.—If the patient survive the stages of the disease already described, the pneumonic process will end in one of four ways.

1. **Resolution.**—The gradual return of the lung to its normal condition is the most frequent termination of croupous pneumonia. This is effected by the fatty degeneration and liquefaction of the inflammatory products which have accumulated within the alveoli. Thus altered, they are removed principally by absorption and, to a less extent, by expectoration. This process is assisted by the return of the blood-vessels to a normal condition and the re-establishment of the circulation.

2. **Gangrene.**—This result is rare, and is chiefly found in drunkards and in persons of debilitated constitution. Two conditions appear to be principally concerned in bringing about this result: (1) the interference with the supply of blood by the formation of coagula in the pulmonary and bronchial vessels, together with considerable hemorrhage into the pulmonary tissue; and (2) the local toxic influence of some special form of septic infection. The gangrene is usually limited to a small area of the pneumonic lung, and is either *diffused* or *circumscribed*. In the former, the exudation and lung-tissue in the gangrenous area form an ill-defined, semi-diffluent, dirty gray, fœtid substance; in the latter, an abscess cavity containing a pulpy slough of similar color and odor.

3. **Abscess.**—The formation of abscess is also a rare result of pneumonia. It occurs under conditions similar to those which predispose to gangrene, which indeed it not infrequently follows. Abscess is commoner in the upper than in the lower lobes. It may follow circumscribed gangrene, or it may arise, as in other places, from the growth of pyogenic cocci without any necrosis visible to the naked eye. When preceded by gangrene, the necrosed tissue may be expelled through the bronchi, and the resulting cavity heal by granulation and cicatrization. Abscesses formed in these ways are usually single, and thus differ from those due to pyæmia.

4. **Chronic Pneumonia.**—If the inflammatory process does not subside, and the exudation is not absorbed, the alveolar walls gradually become thickened by the growth of fibrous tissue. In rare cases the intra-alveolar exudation becomes organized. These changes lead to a general induration of the affected part of the lung. This termination of croupous pneumonia is comparatively rare.

2. Lobular, Catarrhal, or Bronchopneumonia.

Bronchopneumonia is an inflammation of the lung, due to an irritant entering by the bronchi. This irritant gives rise to an inflammation of the smaller bronchi, spreading to the bronchioles and alveoli.

As soon as the substance of the lung is involved the term "broncho-pneumonia" is applicable.

Etiology.—Bronchopneumonia is especially frequent in young children and in aged persons, and often in such cases ends fatally. This result is due to the interference with the entrance of air through the inflamed bronchioles, to the limitation of the oxygenating area, and to the absorption of toxins. The immediate causes of death are, therefore, asphyxia and cardiac failure.

There are many irritants which, gaining access to the air-passages, can excite inflammation of the bronchioles and subsequently of the alveoli. Among these may be mentioned (1) irritant gases; (2) dust of various kinds, such as particles of carbon (p. 488), steel, iron, or stone, which differ in their irritant qualities, and, therefore, in the acuteness of the inflammation to which they give rise; and (3) organisms, of which the most important is the Bacillus tuberculosis—for bronchopneumonia is the principal lesion in pneumatogenous pulmonary tuberculosis (*phthisis*). Not infrequently the growth of the pneumococcus may act as the immediate cause (p. 312). Moreover, septic organisms, conveyed with portions of food or of saliva, may enter the air-passages, especially when the glottis is insensitive or paralyzed. Blood and putrid discharges may be sucked into the bronchi during operations on the mouth or nose, or when they occur in wounds or diseases of these parts. Among other organisms which may enter the lungs by aspiration are the actinomyces and the bacilli of diphtheria and of glanders. (4) Bronchitis, whether simple or occurring in specific diseases such as measles, whooping-cough, and variola, is a common antecedent of bronchopneumonia.

All conditions depressing the general health and strength predispose to bronchopneumonia. Collapse of scattered lobules often seems to precede the inflammation, and, by interfering with the circulation in the affected alveoli, may weaken the resistance of the tissues. But, whenever bronchitis has reached the smallest tubes, extension of the inflammation to the alveoli may occur without collapse.

Pathology.—Bronchopneumonia has been produced experimentally. Animals have been made to inhale irritant gases or suspended particles of various kinds. Further, by division of the vagus, saliva and food have been permitted to enter the air-passages. The resulting changes vary (1) with the *size* of the inhaled particles, and (2) with the *intensity of the irritation* which they are capable of exciting. Thus, very fine particles cause inflammation of widely separated lobules; larger ones block some of the smaller bronchi, and cause collapse and secondary inflammation of lobules—results which have led to the name of "lobular pneumonia." The aspiration of a quantity of septic discharge or other fluid into a bronchus may affect many lobules or even a whole lobe. According to the intensity of the inhaled irritant, the result may vary from slight inflammatory œdema in a collapsed patch, through all

stages of inflammation up to gangrene. In the tubercular form (p. 362) the inflammatory products caseate. Not improbably the three modes in which tuberculosis is conveyed—by the air-passages, by the blood, and by the lymph—also hold good in the case of other forms of bronchopneumonia. In the case of septic wounds which are followed by this affection of the lungs, the infection appears to be conveyed by the lymph or blood.

Morbid Anatomy.—The *bronchi* are always more or less inflamed and contain thick mucus. The lung-tissue contains a varying number of solid patches, due either to (1) *collapse* or to (2) *inflammatory consolidation*. Emphysema, with more or less congestion and œdema, is commonly found in their neighborhood.

Collapsed patches are particularly common in the lower lobe, especially along its thin borders. Sometimes a large portion of a lobe is thus involved; at other times only a few, small, isolated patches. The surface of the collapsed part is depressed below the general surface of the lung. It has a dark bluish color, and is easily inflated from the bronchi. On section, it is dark-red, smooth, and shiny. It is tough and non-crepitant, and portions of it sink in water. On closer inspection the patches are seen to be more or less conical, with their bases toward the surface of the lung and their apices toward the bronchi with which they are in connection. The pleura over a patch of collapsed lung is normal.

Pneumonic patches are of conical form, and are airless, like the collapsed parts; moreover, they are similarly distributed. But the base of a pneumonic patch is raised above, never depressed below, the surface, while the patch forms a less pliable and more nodular mass. Occasionally, when it is of considerable size, its pleural covering may be opaque with inflammatory exudation. On section, pneumonic patches may be clearly defined, but their outlines are generally less distinct than those of collapsed patches; they usually range in size from that of a pea to a hazel-nut. The surface of the section tends to rise slightly above the surrounding tissue: the substance is soft, friable, opaque-looking, smooth or faintly granular, at first dark-red in color, then passing through grayish-red to grayish-yellow—the lighter color being central. A turbid red or grayish juice can be pressed from it. Neighboring lobular patches often blend, and as the diffuse consolidation thus formed becomes paler, firmer and drier, it may occasionally resemble in appearance ordinary gray hepatization. Sometimes the pneumonic process is found involving patches of collapsed lung; these consequently become swollen, opaque, and œdematous.

When bronchopneumonia is so extensive that the consolidation is practically "lobar," it is difficult to distinguish it from acute pneumonia. Evidence of the blending of lobular masses, and especially the presence of outlying patches in the neighborhood of the main mass, are the most important points to look for. The *absence* of adherent inflammatory exudation from the pleural surface is evidence against acute

weakening occurs. Mott's view, that this is due to an endarteritis of the vasa vasorum, which is frequently present, is in many cases highly probable (Fig. 262); but the cause of this endarteritis has then to be elucidated. It is not improbable that the toxines of infective diseases produce the primary injury to the arterial walls in some instances, either acting on the middle coat directly or on the vasa vasorum. In other cases the loss of elasticity may be a true senile change, as it often seems to be in emphysema.

Inflammation of Veins.

Inflammation of veins (*phlebitis*) is very analogous to inflammation of arteries. *Acute infective phlebitis* is decidedly more frequent than acute infective arteritis. In most cases it is due to the presence and growth of organisms (*acute suppurative phlebitis*). The wall of the vein becomes swollen and densely infiltrated with multinucleated leucocytes. All appearance of normal structure is lost, the cells nearest the lumen die and are cast off, as in the wall of an abscess, into which the wall of the vein has been practically converted (Fig. 277). Septic thrombosis follows and, in many cases, pyæmia.

FIG. 277.

Section through a portal canal in a case of suppurative pylephlebitis arising in connection with "umbilical pyæmia." The vein-wall (V) is converted into granulation-tissue. Lumen of vein is below on the left. × 60. (Boyd.)

Non-infective and *proliferative phlebitis* are due to the same causes, and present the same appearances, as the similar affections of arteries. A recurrent phlebitis, especially common in the internal saphenous vein, is frequently met with in gout.

mucoid exudation, as contrasted with the contents of the air-cells in acute pneumonia, which are first blood-corpuscles and fibrin, and, later on, leucocytes; the walls of the alveoli are considerably thickened in bronchopneumonia, much less affected in lobar pneumonia.

Terminations.—**Resolution** is the most common termination. The contents of the alveoli undergo fatty degeneration, and are removed by expectoration and absorption, the lung gradually regaining its normal character. This process, however, is less readily effected than in croupous pneumonia, and it often occupies such a lengthened period that some thickening of the bronchial and alveolar walls, with dilatation of the smaller bronchi, remains. In chronic cases this **fibroid thickening** is more marked, and much irregularly distributed induration may occur accompanied by pigmentation and bronchial dilatation (p. 492). In these chronic forms, **caseation** sometimes affects the alveolar contents, which then become encapsuled, or, in quite exceptional cases, absorbed; but such cases are usually, if not invariably, tubercular.

Hypostatic Pneumonia.—Allusion must be made to a form of consolidation which is often described as pneumonia, but which, for the most part, is not inflammatory in its nature. This is the so-called "hypostatic pneumonia." This condition is met with at the bases and most dependent portions of the lungs in the course of both chronic and acute diseases, and also in the aged and debilitated. It consists in the main of collapse, passive hyperæmia, and œdema of the lung-tissue, resulting from weak inspiratory power, feeble circulation, and gravitation. The consolidation thus mechanically induced is increased by more or less exudation of fluid and blood-corpuscles into the alveoli. This exudation is due to the damage of the walls of the capillaries, caused by the imperfect circulation. The passive hyperæmia of the alveolar walls is accompanied by some desquamation of the endothelial cells; and in chronic cases breaking up of exuded blood-corpuscles results in some pigmentation of the lung-tissue, while the fibrous tissue is increased in amount (*brown induration*).

3. Interstitial or Chronic Pneumonia.

Interstitial or chronic pneumonia is characterized by a gradual increase in the connective tissue of the lung, which leads to thickening of the pulmonary texture and to progressive obliteration of the alveolar cavities. It is commonly associated with catarrh and dilatation of the bronchi, and often with ulceration of the bronchial walls and excavation of the indurated lung (p. 508).

Etiology.—In the large majority of cases interstitial pneumonia is secondary to some inflammation of bronchi, alveoli or pleura: it results also from persistent atelectasis or collapse. It may be stated generally that all inflammatory processes in the lungs, when they become chronic, lead to an increase of the connective tissue, and consequently to fibroid induration of the organs.

tion of the pleura over the inflamed area, and sometimes, owing to the spread of the infection, by that of the peritoneum and pericardium. The bronchial glands are inflamed and swollen, the mediastinal connective tissue is frequently œdematous, and acute secondary meningitis occasionally supervenes. The disease is accompanied by a high temperature, beginning with a sudden rise (p. 230), and ending by crisis; cloudy swelling of organs results. Death, when it occurs, seems to be due to cardiac failure, induced by general poisoning.

Etiology.—This disease was formerly attributed to a chill, and, in certain cases, its connection with exposure to cold and damp is very striking. Exposure is, however, only a predisposing cause, for it occurs in but a small minority of the cases. Moreover, although the disease is most prevalent in the early spring, it does not especially affect those who are most exposed to the vicissitudes of the weather, nor does its prevalence rise and fall with that of bronchitis.

Similarly, depressed health is only a predisposing cause. Typically healthy people are often affected, but it is especially liable to occur as a complication in cases of erysipelas, typhoid fever, chronic alcoholism, and other debilitating diseases. Pneumonia is prone to recur in a person who has once suffered from it.

The disease is occasionally so prevalent as to be practically epidemic. Small outbreaks occasionally occur in wards, prisons, and similar places; the disease is sometimes endemic in a house, from time to time attacking different people in it; but there is in general no evidence that it is contagious.

Pathology.—Acute pneumonia is a general infective disease in which the inflammation of the lung is the characteristic local lesion. This is shown by the typical course of the fever, ending usually in a crisis between the fifth and eighth days, and by the absence of any constant relationship between the extent of the local inflammation and the intensity of the fever. The gravity of the disease is proportional to the intensity of the toxines at work, the actual interference with the respiratory function being only of secondary importance. Death occurs by cardiac failure resulting from the toxæmia, not by deficient aëration of the blood.

In the large majority of cases the disease is due to the growth of the Diplococcus pneumoniæ (p. 311). Less commonly Friedländer's bacillus, streptococci, or the bacilli of tuberculosis, typhoid fever, or diphtheria have been found, especially in pneumonia occurring in the course of other diseases. But even in these secondary pneumonias the

FIG. 278.—Acute lobar pneumonia (red hepatization). Vertical section through left lung. *A, B*, advancing margin of pneumonic area, with hyperæmic edges; *C*, hemorrhagic area; *D*, fissure between upper and lower lobes; *E*, normal lung; *F*, larger bronchi; *G*, bronchial glands with pigment; *H*, consolidated area; *I, I'*, pulmonary vein; *K*, engorged area, showing commencement of pneumonic process. Between *K* and *B* several of these areas may be seen. In this specimen, *contrary to the usual rule*, the pneumonia commenced in the upper lobe and spread downward, death ensuing on the fifth day. $\times \frac{3}{4}$.

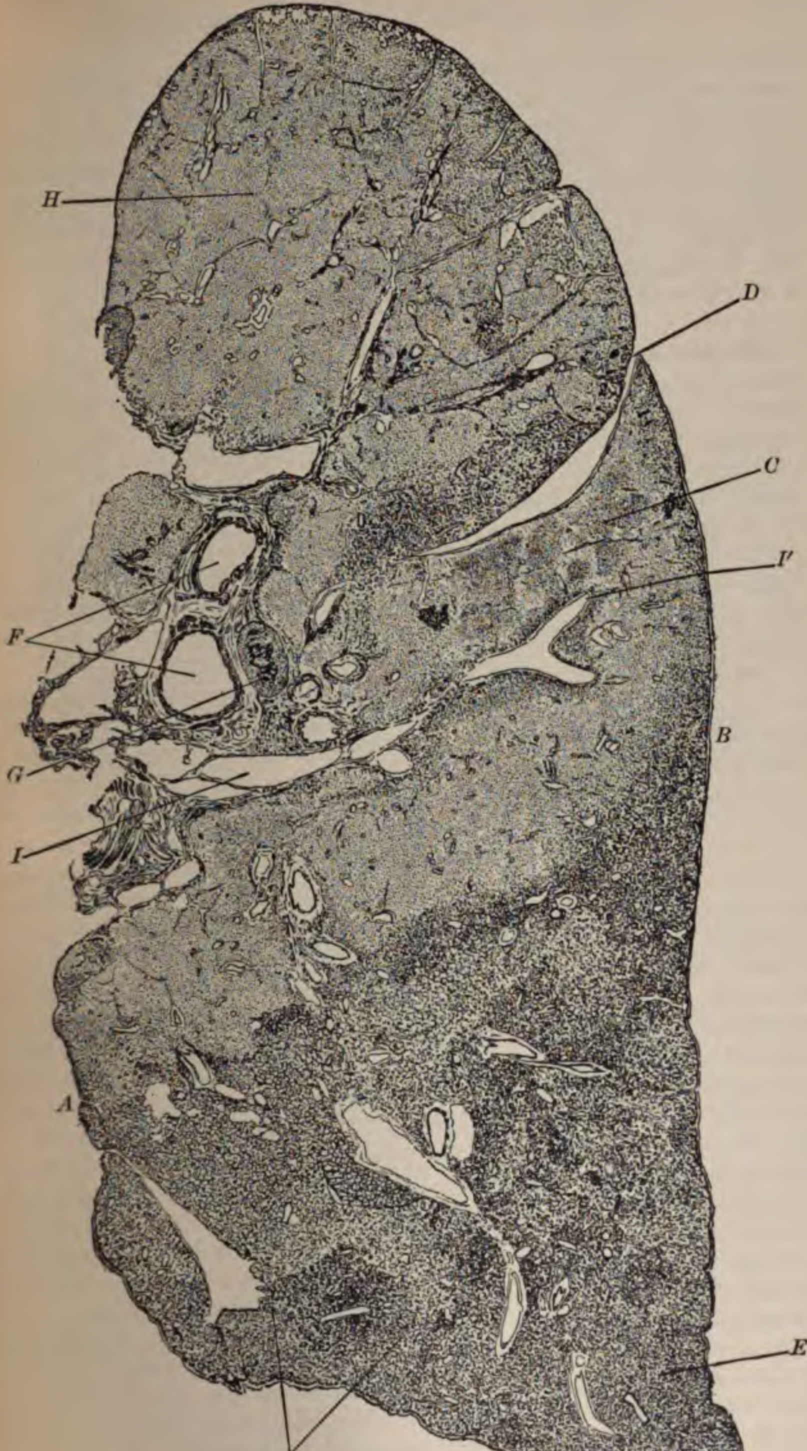


FIG. 278.—For description, see opposite page.

Diplococcus pneumoniæ (pneumococcus) is the organism most frequently met with. The precise method of infection is unknown.

The pneumococcus exists normally in the mouth, and can generally be found on the surface of the tonsils. Indeed, all the organisms just mentioned may be met with in the air-passages of persons free from pneumonia. Experimentally, any of these organisms may be blown into the trachea without causing this disease; but pneumonia follows (1) if dust be simultaneously injected; or (2) if the animals, after being kept warm, are suddenly immersed in a cold bath at the time of the injection.

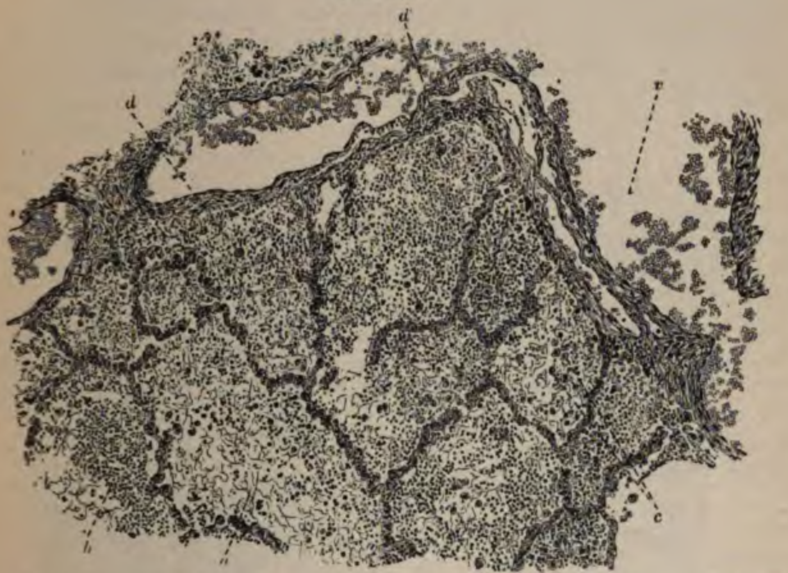
Morbid Anatomy.—The local process is characterized by intense inflammatory hyperæmia of the lung, and by the exudation of a large amount of coagulable material into the pulmonary tissue. It is termed "croupous" from the fibrinous character of the exudation. The term "lobar" is applied to it because it almost invariably affects an extensive portion of the lung. The process is commonly described as consisting of three stages—(1) that of *engorgement*; (2) that of *red hepatization*; and (3) that of *gray hepatization*.

In the *first* stage, that of **engorgement**, small patches of lung-tissue, only visible in large, thin sections, become intensely hyperæmic and rapidly run together to form a large uniformly engorged dark-red area. The weight of this congested portion of the lung is increased, its elasticity is diminished, its substance is less crepitant and more friable than natural, and its surface pits upon pressure. On section, it yields a reddish, frothy, tenacious liquid.

In the *second* stage, that of **red hepatization**, there is an exudation of fluid and blood-corpuscles into the pulmonary tissue. Some of the vessels may also rupture and small extravasations occur. The exuded liquids coagulate within the air-vesicles and terminal bronchioles, and form a semi-transparent coagulum enclosing red corpuscles and leucocytes in its meshes (Fig. 279). The fibrin-filaments, according to Weichselbaum, are much thicker and more numerous in cases due to the Diplococcus pneumoniæ. Contrary to the usual rule in acute inflammations, the uninucleated leucocytes are as plentiful as the multinucleated: both forms may contain pneumococci. The lung is now much heavier than in the preceding stage, and is increased in size, so as to be often marked by the ribs. The affected portion can be recognized before a section is made, for the pleura over it is hyperæmic, opaque, and covered with fibrinous exudation, while the distention, firmness, and dark purple color of the lung beneath cannot escape notice. It is quite solid, sinks in water, and cannot be artificially inflated. It does not crepitate under the fingers, and is remarkably friable, breaking down readily with a soft granular fracture. The cut surface has a granular appearance, seen especially when the tissue is torn. This is owing to the small masses of coagulated exudation, which project from the alveoli they fill. There is no lobulation of the margin of the inflamed area, no outlying racemose nodules or other indication of infection spreading by the bronchi. The color is of a dark reddish-brown, here and there passing into gray.

This admixture with gray sometimes gives a marbled appearance. The red color is due chiefly to vascular engorgement, but partly to extravasated red corpuscles. Throughout this stage the vessels in the alveolar walls are engorged, while the alveolar epithelium is usually swollen and granular. If a section of the spreading edge be examined at this stage, it will be found intensely hyperæmic. The hyperæmia extends irregularly into the adjacent tissue (Fig. 278).

FIG. 279.



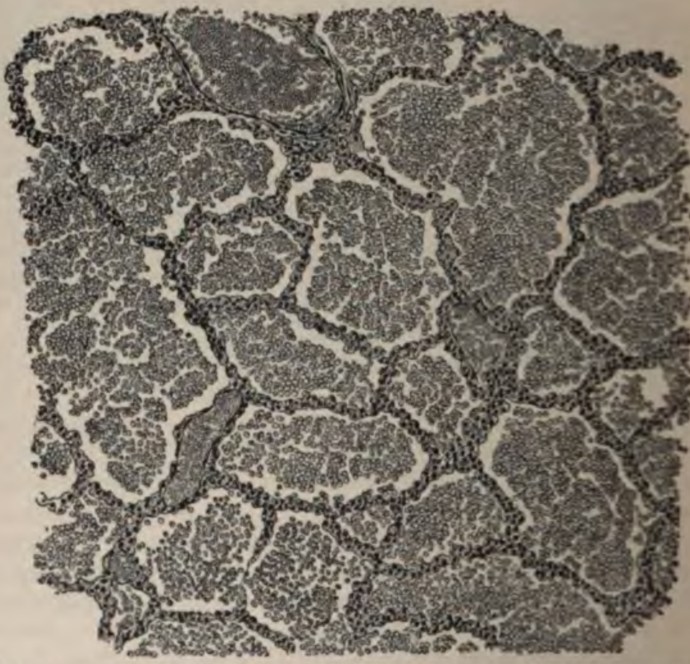
Acute lobar pneumonia (red hepatization). *a*, alveolus containing fibrin-filaments and a few blood-corpuscles; *b*, alveolus containing a larger proportion of corpuscles; *c* and *d*, desquamated alveolar epithelium; *v*, vein. Most of the red blood-corpuscles in the alveoli are stained; those in the vein are unstained. × 120.

The *third* stage, that of **gray hepatization**, is characterized by a marked emigration of leucocytes, and by more extensive degenerative changes in the alveolar epithelium. The walls of the alveoli are infiltrated, and their cavities distended with the emigrated leucocytes. The walls and the contents of the alveoli now assume a uniform appearance, and the granular appearance of the red stage is lost (Fig. 279). The fibrinous material next disintegrates, and the white cells rapidly undergo fatty changes, whilst the red are decolorized, so that the alveoli are seen to be full of granular elements, which in many parts have lost their distinctive outlines (Fig. 280). Occasionally, when this stage is unusually advanced, the alveolar walls may be found, here and there, partially destroyed. The weight, density, and friability of the lung are now even greater than in the stage of red hepatization. The tissue is soft and pulpy, and a puriform liquid exudes from its cut surface. The most prominent feature, however, is the difference in the color of the organ. Instead of

a dark, redish-brown color, the section now appears a gray or yellowish-white, marbled by the tracts of pigment-bearing connective tissue. The pallor is owing partly to the fatty degeneration which the cells have undergone, and partly to the pressure exercised upon the bloodvessels by the exuded substances and newly formed cells; but since Rindfleisch has shown that it is always easy to inject the vessels, it would seem likely that a good deal of the pallor is due to the fall in blood-pressure after death. The stage of gray hepatization, when far advanced, has been termed "suppuration, or purulent infiltration, of the lung." This, in all probability, only occurs in fatal cases.

Although these three stages of the pneumonic process have been described as succeeding one another in orderly succession, it must be remembered not only that each stage does not occur simultaneously

FIG. 280.



Acute lobar pneumonia (gray hepatization). Lobules full of degenerating leucocytes and fluid exudation; and two veins full of red blood-corpuscles. × 100.

throughout the whole of the affected area of the lung, but that in some cases it is more accurate to speak of only two stages—*engorgement* and *hepatization*. Patches of gray hepatization may be found in recently invaded parts of the lung, and patches of red hepatization in those portions which were earliest affected. The exact characters of these changes not improbably depend on the presence of centres of infection, on the nature and virulence of the organisms present, and on the local conditions influencing their growth. According to this explanation, the *exudation* first filling the alveoli remains unaltered until degeneration

nd disintegration set in. The bronchi in the affected area are always iflamed, and usually contain a viscid, blood-stained, rust-colored mucus, 'hich forms the characteristic expectoration. Sometimes the sputum dark and watery, like prune-juice. This is probably owing to the ldition of serous exudation from neighboring parts of the lung.

Terminations.—If the patient survive the stages of the disease ready described, the pneumonic process will end in one of four ways.

1. **Resolution.**—The gradual return of the lung to its normal contion is the most frequent termination of croupous pneumonia. This effected by the fatty degeneration and liquefaction of the inflammary products which have accumulated within the alveoli. Thus altered, ey are removed principally by absorption and, to a less extent, by pectoration. This process is assisted by the return of the bloodssels to a normal condition and the re-establishment of the circulation.

2. **Gangrene.**—This result is rare, and is chiefly found in drunkards id in persons of debilitated constitution. Two conditions appear to principally concerned in bringing about this result: (1) the interrence with the supply of blood by the formation of coagula in the ulmonary and bronchial vessels, together with considerable hemorrhage ito the pulmonary tissue; and (2) the local toxic influence of some ecial form of septic infection. The gangrene is usually limited to a nall area of the pneumonic lung, and is either *diffused* or *circumscribed*. 1 the former, the exudation and lung-tissue in the gangrenous area rm an ill-defined, semi-diffluent, dirty gray, fœtid substance; in the tter, an abscess cavity containing a pulpy slough of similar color and lor.

3. **Abscess.**—The formation of abscess is also a rare result of pneuonia. It occurs under conditions similar to those which predispose gangrene, which indeed it not infrequently follows. Abscess is ommoner in the upper than in the lower lobes. It may follow cirumscribed gangrene, or it may arise, as in other places, from the rowth of pyogenic cocci without any necrosis visible to the naked eye. Vhen preceded by gangrene, the necrosed tissue may be expelled rough the bronchi, and the resulting cavity heal by granulation and icatrization. Abscesses formed in these ways are usually single, and hus differ from those due to pyæmia.

4. **Chronic Pneumonia.**—If the inflammatory process does not subide, and the exudation is not absorbed, the alveolar walls gradually ecome thickened by the growth of fibrous tissue. In rare cases the itra-alveolar exudation becomes organized. These changes lead to general induration of the affected part of the lung. This terminaion of croupous pneumonia is comparatively rare.

2. Lobular, Catarrhal, or Bronchopneumonia.

Bronchopneumonia is an inflammation of the lung, due to an irriant entering by the bronchi. This irritant gives rise to an inflammaion of the smaller bronchi, spreading to the bronchioles and alveoli.

As soon as the substance of the lung is involved the term "broncho-pneumonia" is applicable.

Etiology.—Bronchopneumonia is especially frequent in young children and in aged persons, and often in such cases ends fatally. This result is due to the interference with the entrance of air through the inflamed bronchioles, to the limitation of the oxygenating area, and to the absorption of toxins. The immediate causes of death are, therefore, asphyxia and cardiac failure.

There are many irritants which, gaining access to the air-passages, can excite inflammation of the bronchioles and subsequently of the alveoli. Among these may be mentioned (1) irritant gases; (2) dust of various kinds, such as particles of carbon (p. 488), steel, iron, or stone, which differ in their irritant qualities, and, therefore, in the acuteness of the inflammation to which they give rise; and (3) organisms, of which the most important is the Bacillus tuberculosis—for bronchopneumonia is the principal lesion in pneumatogenous pulmonary tuberculosis (*phthisis*). Not infrequently the growth of the pneumococcus may act as the immediate cause (p. 312). Moreover, septic organisms, conveyed with portions of food or of saliva, may enter the air-passages, especially when the glottis is insensitive or paralyzed. Blood and putrid discharges may be sucked into the bronchi during operations on the mouth or nose, or when they occur in wounds or diseases of these parts. Among other organisms which may enter the lungs by aspiration are the actinomyces and the bacilli of diphtheria and of glanders. (4) Bronchitis, whether simple or occurring in specific diseases such as measles, whooping-cough, and variola, is a common antecedent of bronchopneumonia.

All conditions depressing the general health and strength predispose to bronchopneumonia. Collapse of scattered lobules often seems to precede the inflammation, and, by interfering with the circulation in the affected alveoli, may weaken the resistance of the tissues. But, whenever bronchitis has reached the smallest tubes, extension of the inflammation to the alveoli may occur without collapse.

Pathology.—Bronchopneumonia has been produced experimentally. Animals have been made to inhale irritant gases or suspended particles of various kinds. Further, by division of the vagus, saliva and food have been permitted to enter the air-passages. The resulting changes vary (1) with the *size* of the inhaled particles, and (2) with the *intensity of the irritation* which they are capable of exciting. Thus, very fine particles cause inflammation of widely separated lobules; larger ones block some of the smaller bronchi, and cause collapse and secondary inflammation of lobules—results which have led to the name of "lobular pneumonia." The aspiration of a quantity of septic discharge or other fluid into a bronchus may affect many lobules or even a whole lobe. According to the intensity of the inhaled irritant, the result may vary from slight inflammatory œdema in a collapsed patch, through all

stages of inflammation up to gangrene. In the tubercular form (p. 362) the inflammatory products caseate. Not improbably the three nodes in which tuberculosis is conveyed—by the air-passages, by the blood, and by the lymph—also hold good in the case of other forms of bronchopneumonia. In the case of septic wounds which are followed by this affection of the lungs, the infection appears to be conveyed by he lymph or blood.

Morbid Anatomy.—The *bronchi* are always more or less inflamed nd contain thick mucus. The lung-tissue contains a varying number f solid patches, due either to (1) *collapse* or to (2) *inflammatory consolidation*. Emphysema, with more or less congestion and œdema, is ommonly found in their neighborhood.

Collapsed patches are particularly common in the lower lobe, specially along its thin borders. Sometimes a large portion of a lobe s thus involved; at other times only a few, small, isolated patches. The surface of the collapsed part is depressed below the general surface f the lung. It has a dark bluish color, and is easily inflated from the ronchi. On section, it is dark-red, smooth, and shiny. It is tough nd non-crepitant, and portions of it sink in water. On closer inspecion the patches are seen to be more or less conical, with their bases oward the surface of the lung and their apices toward the bronchi vith which they are in connection. The pleura over a patch of colapsed lung is normal.

Pneumonic patches are of conical form, and are airless, like the ollapsed parts; moreover, they are similarly distributed. But the ase of a pneumonic patch is raised above, never depressed below, the urface, while the patch forms a less pliable and more nodular mass. Occasionally, when it is of considerable size, its pleural covering may e opaque with inflammatory exudation. On section, pneumonic atches may be clearly defined, but their outlines are generally less istinct than those of collapsed patches; they usually range in size rom that of a pea to a hazel-nut. The surface of the section tends to ise slightly above the surrounding tissue: the substance is soft, friable, paque-looking, smooth or faintly granular, at first dark-red in color, hen passing through grayish-red to grayish-yellow—the lighter color eing central. A turbid red or grayish juice can be pressed from it. Neighboring lobular patches often blend, and as the diffuse consolidaion thus formed becomes paler, firmer and drier, it may occasionally esemble in appearance ordinary gray hepatization. Sometimes the neumonic process is found involving patches of collapsed lung; these onsequently become swollen, opaque, and œdematous.

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pneumonia; but it must be remembered that as such exudation may form over a bronchopneumonic area, its *presence* is of little pathognomonic importance.

In *septic* bronchopneumonia—the commonest cause of death after operations on the jaw, mouth, and pharynx—the pneumonic patches suppurate. The *abscesses* thus formed are sometimes fœtid and contain sloughs of lung-tissue: such sloughs are surrounded by more or less extensive consolidation; and inflammatory hyperæmia and œdema of the lung are marked.

Microscopically, in the earliest red stage, the alveoli contain fluid, red corpuscles, and a few leucocytes, while the alveolar epithelium is swollen and granular. The alveoli rapidly become filled with a cell-mass, consisting of leucocytes and desquamated epithelium in varying proportions—leucocytes being in excess in the more acute (Fig. 281),

FIG. 281.

Bronchopneumonia. Showing thickening of the walls of the alveoli by multiplication of cells and desquamation of the latter into the alveoli, along with mucus and some leucocytes. The alveolar wall is breaking down.

and epithelial cells in the more chronic forms. In the most acute cases (*septic bronchopneumonia*), either suppuration and sloughing occur, or hemorrhagic exudation with subsequent gangrene.

Contrast with Lobar Pneumonia.—In bronchopneumonia the onset is gradual and the termination by lysis, as opposed to the sudden onset and critical defervescence of lobar pneumonia; the temperature is of the remittent or intermittent type, instead of a continued pyrexia; the consolidation is lobular, instead of lobar, in distribution; the alveoli are filled chiefly with desquamated endothelial cells, leucocytes and

ıcoid exudation, as contrasted with the contents of the air-cells in ıte pneumonia, which are first blood-corpuscles and fibrin, and, later , leucocytes; the walls of the alveoli are considerably thickened in onchopneumonia, much less affected in lobar pneumonia.

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Congenital syphilis gives rise to a gummatous inflammation, and also to a diffuse interstitial pneumonia (*white pneumonia*). The latter is characterized by fibrosis with proliferation and desquamation of the alveolar epithelium. In adults, syphilitic changes in the lung are probably rare; but it is impossible to be certain of the nature of some localized fibroid changes.

The chief causes of interstitial pneumonia are:

1. **Croupous Pneumonia.**—The consolidation of acute croupous pneumonia usually undergoes complete and rapid resolution; but occasionally this is more protracted. Then the hepatized lung tends to become slightly indurated, mainly owing to thickening of the walls of the alveoli, and sometimes to organization of their contents. This indurated hepatization differs but little in its physical characters from ordinary red and gray hepatization; the lung is, however, firmer, more resistant, and less granular.

2. **Bronchopneumonia.**—Bronchopneumonia is a more frequent cause than the preceding. The greater liability of this form of pneumonia to lead to pulmonary induration is to be accounted for partly by its longer duration and greater tendency to become chronic, and partly by the existence of bronchial dilatation, with which it is so frequently associated (p. 492). The existence of this dilatation favors the persistence of the catarrhal and pneumonic process. The removal of secretion is rendered difficult; and the retained secretion tends to keep up and increase the irritative process both in the dilated bronchi and the alveoli, and this persistence of the bronchial and pulmonary inflammation leads to fibroid thickening of the bronchial and alveolar walls. In this way areas of fibroid induration are produced, which, as the process extends, may ultimately involve large portions of the lung. The progressive tendency of the process is, probably, partly to be explained by the fact that pulmonary fibrosis is itself a cause of bronchial dilatation. When, therefore, fibrosis is once established, the new tissue in contracting induces further dilatation of the bronchi; and this, again, as before explained, favors the still further extension of the bronchial and pulmonary induration.

Under this head may also be included those cases of induration and ulceration of the lung which result from *obstruction of a main bronchus*—such as is produced by the pressure of an aneurism. Here the retained bronchial secretion sets up inflammatory changes in the bronchial and alveolar walls, which gradually lead to induration and ulceration of the lung.

3. **The Inhalation of Solid Irritating Particles.**—This is the commonest cause of interstitial pneumonia, leading to the fibrosis of the lung so common among miners, potters, stonemasons, grinders, and others. The continuous irritation of the inhaled particle induces a bronchial and alveolar inflammation, and ultimately a progressive fibrosis, with dilatation and ulceration of the bronchi (p. 508). Such cases often become tuberculous.

4. **Pleurisy.**—This, in exceptional cases, leads to the development of an interstitial pneumonia. Such a result is most likely to occur in those cases of pleurisy which are more or less chronic, and in which the effu-

sion remains long unabsorbed. The induration thus induced is often partial, consisting merely in an increase of the interlobular connective tissue, originating and extending inward as dense bands from the thickened visceral pleura. In other cases, pleurisy gives rise to a much more general fibrosis.

5. **Atelectasis,** or failure of part of the lung to expand after birth, and **persistent collapse** lead to marked fibrosis of the affected area. Later on, bronchiectasis and obliteration of most of the alveoli occur. The original positions of the latter may be merely indicated by a few epithelial cells.

Morbid Anatomy.—The appearances presented by the lung, when

FIG. 282.

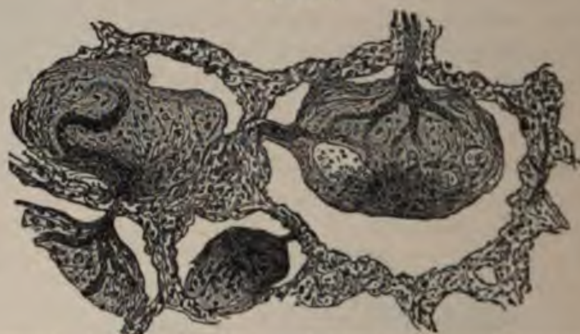
Interstitial pneumonia. From a case of unilateral "fibrosis" of the lung. The bronchi were much dilated, and there was a complete absence of any caseous change. The drawing shows the new fibrous growth, both in the alveolar walls (*b*) and in the interlobular tissue (*c*), also the pigmentation. At (*a*) a divided artery is seen. With a higher power, a delicate reticulum is visible between the cell-elements. $\times$ 100.

the fibrosis is general and well advanced, are very characteristic. The organ is diminished in size; the tissue is smooth, dense, firm—in parts almost cartilaginous in consistence—and is irregularly mottled with black pigment. The alveolar structure of the lung is in most part completely destroyed, and on section the dilated bronchi are seen as numerous large openings scattered over its surface. These dilated bronchi frequently become the seats of secondary inflammatory processes, which may lead to ulceration and ultimately to extensive excavation of the indurated tissue; but there is a complete absence of any of those caseous changes which are so characteristic of pulmonary tuberculosis. This secondary inflammation of the dilated bronchi is induced by the irritating and often putrid secretion which they contain, and which is, as a rule, incompletely removed by expectoration. The pleura is considerably thickened and generally adherent.

Microscopically, fibrous tissue is found in the interalveolar, peribronchial, and interlobular connective tissue. This new growth, as it increases and contracts, gradually replaces and obliterates the alveolar

structure. The character of these changes, however, varies somewhat according to the nature of the cause. When the result of a *croupous pneumonia*, the primary change takes place in the walls of the alveoli (Fig. 282), although ultimately the interlobular tissue is involved. The

FIG. 283.



Chronic pneumonia. Showing organization of intra-alveolar exudation-products. Bloodvessels are seen distributed in the exudation-products; these bloodvessels communicate with those in the alveolar walls. The alveolar walls are also thickened by a fibrous growth. × 120.

alveolar walls become thickened by the growth of fibrous tissue. The new-growth, in its earlier stages, contains new bloodvessels, but later on the tissue contracts, and many of these are destroyed. The alveolar cavities which are not obliterated are either empty or contain exudation-products or a few epithelial cells. Cases occur in which, in addition to the growth in the alveolar walls, the intra-alveolar exudation becomes organized. There is nothing peculiar in the macroscopic characters of the lungs, and many of the alveoli are filled with leucocytes and a fibrin-

FIG. 284.

Chronic pneumonia. A portion of the intra-alveolar exudation-products (Fig. 283) more highly magnified. Showing the elongated spindle-cells, the fibrillation, and bloodvessels containing blood-corpuscles. × 250.

ous meshwork, similar to that met with in red hepatization (Fig. 279). The contents of some of the alveoli differ, however, in this respect—

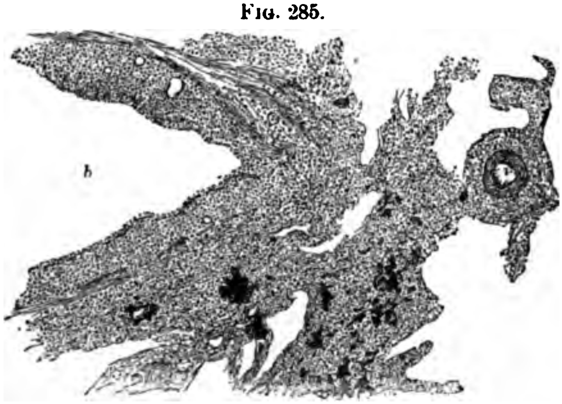
that many of the cells are long and spindle-shaped, and bloodvessels are distributed among them, communicating with those in the alveolar walls (Figs. 283 and 284). These changes are often confined to the parts adjacent to the pleura. The affected areas are ill defined, as they pass gradually into the normal lung-tissue.

When the fibrosis is secondary to an ordinary *bronchopneumonia*, or to that induced by the *inhalation of irritating solid particles*, the alveolar walls are also involved, though the peribronchial and interlobular connective tissue plays a more prominent part in the process (Fig. 285).

The *pleurogenic* form results chiefly from empyemata. In these cases the new fibrous tissue extends inward in bands along the interlobular lymphatic vessels, which communicate freely with those of the thickened pleura; thence it spreads to the peribronchial tissue. The lung is thus surrounded by a dense capsule, and a meshwork of anastomosing fibrous bands permeates its substance, obliterating many of the alveoli and leading to bronchiectasis. More or less bronchitis is usually present.

Atelectasis and *collapse* are said to lead first to slight hemorrhages.

FIG. 285.



Chronic bronchitis and bronchiectasis. Showing the growth of fibrous tissue around the bronchus (b), and the way in which this tissue is invading the walls of the adjacent alveoli; r, a divided artery. × 50.

The subsequent changes in the hæmoglobin lead to the formation of some of the black pigment usually found in fibroid areas due to this cause (p. 487). The alveolar walls become fibrous, the epithelium is more or less shed, and the surfaces of the walls ultimately cohere.

Vesicular Emphysema.

Vesicular emphysema consists essentially in a *permanent* overdistention of the infundibula and air-cells due to atrophy of the intervening septa and to general diminution in the elasticity of the lungs. It should be distinguished from the acute overdistention often seen, especially in children, after death from bronchitis or whooping-cough.

The condition of the lungs met with in these diseases is sometimes called "acute emphysema."

Varieties.—Two varieties are described: (1) Hypertrophic or "large-lunged" emphysema—by far the most important, and always indicated when the term "emphysema" alone is used; (2) Atrophic, small-lunged, or senile emphysema.

1. In **hypertrophic emphysema** the lungs are enlarged, sometimes so much that they actually cross in the mid-line in front, obliterate the superficial cardiac dulness, project into the neck, and push down the diaphragm. Owing to the loss of their elasticity the lungs collapse but slightly when the chest is opened, and their usually sharp edges (in front and round the base) are pale, thick, round, and more or less irregular from the protrusion of soft, pale, rounded swellings. Similar swellings frequently project toward the diaphragm; the tongue-like piece of the left lung below the notch is often extremely swollen, and the lungs may bear distinct grooves corresponding to the ribs. Everywhere, in advanced cases, the air-cells are seen through the visceral pleura with abnormal distinctness; but the apices and sharp edges are first and chiefly affected, and spaces of considerable size are here met with. Abnormal pigmentation is usual. The lungs feel much like a

FIG. 286.

Emphysema of the lung (from a case of chronic bronchitis). A portion of the rounded anterior edge of the lung. The varied size of the cavities formed by distention of the alveoli and atrophy of the partitions is well shown. × 8.

down-pillow, they "pit" easily, and crepitate but little. On section, the emphysematous parts are pale, dry and bloodless, and when large

spaces are present in the part cut, the collapse of the affected area is very marked.

Microscopic investigation shows: that the dilatation commences in the infundibula, and extends thence into the alveoli opening into it; that the interalveolar septa atrophy and ultimately become perforated, their elastic fibres yielding and then disappearing; that the stretched capillaries become thrombosed, and then likewise vanish. The apertures in the interalveolar septa enlarge; and others form later between the infundibula: thus are developed irregular cavities, which are sometimes as large as a filbert. The largest are situated in the pale, rounded, bleb-like swellings. Fatty degeneration of the alveolar epithelium is commonly present, and is probably secondary to vascular disturbance.

The obliteration of capillaries in the stretched or destroyed alveolar walls necessarily causes some obstruction to the pulmonary circulation. This is followed by hypertrophy of the right ventricle of the heart. By this means the increased resistance in the pulmonary circulation is overcome (p. 448). The communications between the pulmonary and bronchial vessels become dilated. The connective tissue round the smaller bronchi may be increased as the result of bronchitis.

Results.—The atrophy of the elastic tissue of the lung, by diminishing the expiratory movements of the chest, lessens the normal interchange of gases. As a result, the blood, which is thus inefficiently aërated, stimulates the respiratory centre to an unusual degree, and thus gives rise to deeper inspirations, which, in the absence of the normal elasticity of the lungs, lead to a permanent enlargement of the thorax—the so-called "barrel-shaped chest."

2. **Atrophic emphysema** occurs usually in thin old people who seem to be undergoing general atrophy. The lungs during life may leave the heart unduly exposed; when the thorax is opened they collapse excessively, falling together "like an inflated bag of wet paper" (Jenner). They are excessively pigmented, and their apices and borders, even after collapse has occurred, usually show appearances like those in the large-lunged variety, and are due to similar naked-eye and microscopic changes. In this form, apparently, the elastic tissue is not so generally affected as in the hypertrophic variety.

Etiology.—All conditions which (1) increase the pressure on the inside of the air-vesicles, (2) which withdraw the support normally furnished by the surrounding parts, or (3) which weaken the alveolar walls, may act as causes of emphysema.

1. **Increase of Intra-alveolar Pressure.**—Increased pressure in the air-cells may be due to violent expiratory efforts with closed glottis, as in coughing; to violent muscular efforts in which the glottis is closed and the thorax distended; and to the blowing of wind instruments. Those parts of the lungs which are least supported—the apices and edges—will be most distended. This is the *expiratory theory* of Jenner. Emphysema due to these causes may be *primary*, but more often is associated with chronic bronchitis.

2. Withdrawal of External Support from Alveoli.—By reason of collapse, compression, or consolidation, the entrance of air into, and the consequent expansion of, any part of a lung may be interfered with. Such portions will, during inspiration, afford less support to the air-cells in their immediate neighborhood, and these air-cells will therefore tend to become more distended than those in other parts. Similarly, when from the same cause a whole lung fails to expand, its fellow stretches over toward it, and even the mediastinal contents may be displaced in the same direction. This form of emphysema is termed *vicarious*, *compensatory*, or *secondary*, and this explanation of its causation is known as the *inspiratory* theory. It is frequently found in the neighborhood of localized fibroid changes (p. 480).

3. Weakening of the Alveolar Walls.—This weakening may be due to (*a*) the atrophy and loss of elasticity which accompany old age—the most important element in the causation of atrophic emphysema; (*b*) atrophy following the stretching, narrowing, and obliteration of the bloodvessels, which in its turn is a result of overdistention of the air-cells from any of the causes before mentioned; and (*c*) inherited weakness (emphysema may run in families), or weakness due to some interference with their nutrition, from the mode of living or other causes (p. 44).

Bronchiectasis.

In many different varieties of chronic lung-disease the bronchial tubes are occasionally found dilated. The dilatations are most frequently found in the lower lobes, and may be cylindrical, fusiform, or sacculated. In some cases the most casual inspection shows the relationship of the dilatation to the ordinary tube; in others, it is only the gradual expansion of the bronchial tube on each side of the resulting cavity, and the discovery, microscopically, in the tissue surrounding the latter, of some of the rudiments of the original bronchial wall that elucidate the nature of the lesion. This is especially the case in some instances of the sacculated form, in which the cavities are large and irregular, and their walls composed principally of fibrous tissue.

The causation of bronchiectasis is, in great measure, analogous to that of emphysema. The principal forces concerned are three: (1) increased pressure within the lumen of the tube tending to dilate it at its weakest points—such pressure occurring during either inspiration or expiration; (2) weakening of the wall of the tube through atrophy, inflammation, or ulceration; and (3) traction upon the walls of the tubes exerted by bands of cicatricial tissue in the lungs. These forces usually act in combination; it will therefore be necessary to consider them together.

The only good examples of bronchiectatic cavities due solely to changes in pressure occur in those cases of congenital atelectasis in which the alveoli, in the whole or part of a lung, are unable to expand. The act of inspiration, by causing a flow of air into all those parts in

direct communication with the trachea, not only distends each normal alveolus, but also thereby affords support to those in its immediate neighborhood. Those alveoli immediately in contact with the imperfectly developed portion of the lung will undergo emphysematous changes. The resistance, however, which the young elastic tissue offers to this overdistention will in the same way, by lessening the support, cause dilatation of the pervious bronchial tubes imbedded in the interior of the unexpanded portions. These bronchial tubes will accordingly become gradually distended, and may frequently develop club-shaped terminations.

Acute or chronic inflammation of the bronchial tubes, especially in children, is often accompanied by a slight amount of dilatation of the cylindrical or fusiform type, combined with slight emphysema. This depends partly on the inflammatory weakening of the muscular and elastic tissues in the walls of the bronchial tubes, and partly upon the increased expiratory pressure in coughing, combined with the traction exerted, especially during inspiration, by the ordinary elastic tissue of the lung. Should, however, septic organisms lodge in a tube so dilated, and, by setting up a slow suppurative inflammation, still further weaken a portion of its wall, the forces just mentioned will lead to the formation of an extensive cavity, with ragged, irregular walls. As a rule, however, inflammatory changes in the bronchial tubes do not lead to much dilatation unless there is, in addition, some obstruction to the entry of air into the alveoli. This combination is well illustrated in the local bronchiectasis —not uncommon in children—which occurs as a result of bronchopneumonia or persistent collapse of the lung. In such cases, the air being unable to enter the alveoli, tends, during inspiration, to dilate the tubes, the walls of which are weakened by the bronchitis, and unsupported by properly filled surrounding alveoli. The accompanying cough will act still more effectively in the same way; for during expiration the air, which would by this means ordinarily be driven into and overdistend the alveoli, would, under these conditions, tend instead to dilate the weakened tubes. As a result, the affected portion of lung presents, on section, a large number of small holes about one-eighth of an inch or more in diameter. Should the inflammation become chronic this dilatation will become more pronounced: partly because chronic inflammation, when it affects the bronchial tubes, leads, as it does elsewhere, to replacement of the muscular and elastic elements by a connective tissue, which is easily stretched in its early stages; and partly because there is an increase in the interstitial fibrous tissue of the lung which, later on, tends, as it contracts, to pull upon the walls of the tubes, as explained below.

The contraction of chronic inflammatory fibrous tissue throughout the lung is often regarded as an important factor in the production of chronic bronchiectasis. In the repair-stage of all chronic inflammatory diseases of the lungs fibrous tissue of this type is found. In the large majority of these diseases the pleural surfaces are adherent, so that the fibrous tissue is firmly attached on each side. In these cases the contraction of the new tissue should, theoretically, lead to a rise in the

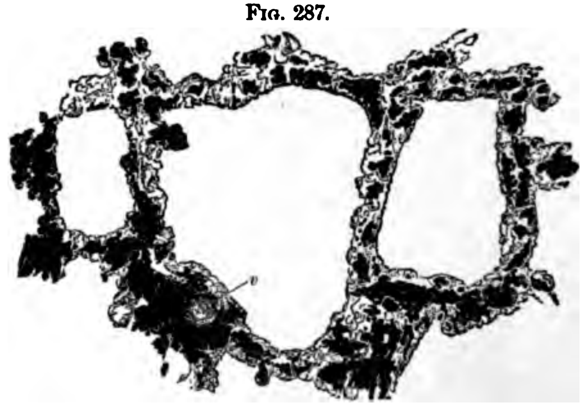
level of the diaphragm ; the sinking in of the wall of the chest ; the dilatation of the bronchial tubes ; and, if the disease is unilateral, to displacement of the mediastinum. In some cases all these changes actually occur, sometimes one and sometimes another being the most prominent. This contracting fibrous tissue will act at greatest advantage during inspiration, when the movements of the chest and diaphragm tend to enlarge all the diameters of the lung.

The contents of bronchiectatic cavities are chiefly mucus, putrefactive organisms, and tissue-débris. Stagnation of the secretion in the dilated tubes is favored by the destruction of nerve-terminals in their walls, brought about by chronic inflammation. The accumulating secretion thus sets up no irritation until it reaches a sound portion of the bronchus : cough is then excited and the irritant expelled. The stagnating secretion undergoes putrefaction, and consequently has, as a rule, an extremely offensive odor.

Pneumoconiosis.

Ordinary atmospheric air always contains dust. When the amount of dust inhaled is comparatively small, it gives rise to pigmentation of the lungs without apparently producing any injurious effects. This pigmentation, absent at birth, gradually increases with advancing age, especially in the case of those who dwell in towns.

FIG. 287.



Pigmentation of the lung. From a woman, æt. sixty-five, with slight emphysema. Showing the situation of the pigment in the thickened alveolar walls, and around the bloodvessel (v). The walls of the latter are also thickened and its lumen diminished. × 100.

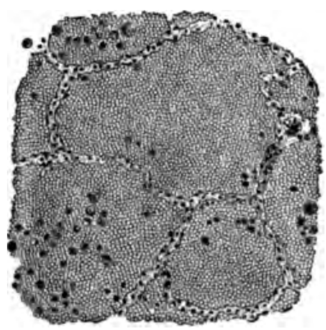
Pigmentation of the lungs is principally due to the presence of particles of carbon and other substances inhaled with the inspired air. These may be arrested in the smaller bronchial tubes or, when the fullest inspiration follows the most extreme expiration, be drawn into the alveoli. In both of these places they may be taken up by leucocytes. Many of these are expelled in the grayish-black sputum frequently expectorated in the early morning (Fig. 289), but a large number penetrate into the alveolar walls and into the interlobular tissue. Most

of the pigment is found contained within the connective-tissue cells or free among the fibres.

The means by which the particles of carbon make their way into the interalveolar tissue is explained in different ways. (1) The branched connective-tissue cells of the alveolar walls send processes, consisting of a greater or less portion of their bodies, between the epithelial cells of the alveolus into the alveolar cavity. As these connective-tissue cells lie in the serous canals which constitute the commencement of the perivasal lymphatics and are themselves phagocytic, it is easy to understand how readily they may serve as the principal carriers by which the particles are withdrawn from the alveoli and conveyed to neighboring parts of the lung. When once the carbon has made its way into the interlobular tissue, some of it is taken up by the fixed cells in this situation, whilst the remainder passes on to the lymphatics and is deposited in the bronchial lymphatic glands, in which black particles are also found. (2) Wandering phagocytic leucocytes (p. 181) are found in the small bronchi and alveoli (Fig. 288). They probably convey particles into the tissue and lymphatics of the lungs.

In many occupations the respired air contains an altogether abnormal proportion of dust, often consisting of some special material, such as coal, stone, iron, or other substances. The first result of breathing air overcharged with such particles is the production of chronic bronchial

FIG. 288.



Alveoli filled with red corpuscles and a few leucocytes containing air-borne pigment. × 120.

catarrh from the mechanical irritation of the mucous membrane of the bronchi. This leads to frequent coughing, followed by deep inspirations, and, therefore, to the aspiration of similar particles into the alveoli. Inflammatory changes in the alveoli follow; leucocytes escape; the cells of the epithelial lining proliferate and many are thrown off. Cells, charged with the inhaled particles, are found free in the alveoli. Some of these cells may be expectorated, but most are absorbed as just described. In the tissues further changes may gradually take place, according to the nature and number of particles deposited. These changes comprise chronic inflammatory thickening of the alveolar walls (Fig. 287), patches of bronchopneumonia, and general increase of the fibrous tissue throughout the organ. Furthermore, these changes render

the affected parts especially liable to invasion by tubercle-bacilli and other parasites.

In the case of miners the particles of coal enter the lungs in such large quantities as to give to them an almost uniform black color (*anthracosis*).[1] The black color of the lungs in these cases is not entirely due to the presence of the inhaled substances, but partly to that of altered blood-pigment. The inflammatory changes in the bronchi and pulmonary tissue already referred to cause marked consolidation of the lungs, which thus become tough and fibrous. In the most severe forms, ulceration, starting from the bronchi, produces cavities (*colliers' and knife-grinders' phthisis*). Owing to these structural changes there is a considerable escape of red corpuscles from rupture of capillaries or inflammatory exudation, and hence a large formation of pigment, to which much of the dark color of these lungs must undoubtedly be ascribed. The lungs of stonemasons (*silicosis*)[2] and grinders (*siderosis*)[3] are, like those of miners, deeply pigmented, though to a less degree; but the black color in the former cases cannot be accounted for on the supposition that it is due to the presence of inhaled particles, for the particles are pale or rust-colored, as the case may be. Carbon-particles are black, angular, and very variable in size and shape. They are unaffected by strong acids and alkalies. Pigment derived from the blood is generally brownish and granular: it is rarely met with in a crystalline form.

Pigmentation of the lungs from the presence of hæmatoidin occurs as the result of many other morbid conditions, many diseases of these organs being attended by the formation of pigment. In *chronic phthisis*, pigmentation occurs, partly as the result of the inflammatory process, and partly from the obstruction of the vessels caused by the new tissue: lines of pigment are constantly seen surrounding the nodules of consolidation. In *acute croupous pneumonia*, the blood which is extravasated into the air-vesicles, and which in the early stages gives to the expectoration a rusty or prune-juice color, subsequently gives rise to pigment, and the sputum consequently becomes grayish-black, the pigment-granules being visible in the desquamated cells. The cells met with in the sputum of *bronchitis* also contain granules of pigment (Fig. 289); and pigmentation plays an important part in the condition of the lungs known as *brown induration* (p. 203). In all cases in which hæmatogenous pigment is found in any quantity in the lung, it is also found in the bronchial glands. It is taken up by the lymphatics, and, like the inhaled carbon, becomes arrested in its passage through these glands, where it remains permanently.

FIG. 289.

Cells from the sputum of bronchitis. Showing the minute granules of pigment within the cells. Some of the cells also contain a few fatty particles. × 400.

[1] Greek ἄνθραξ, cinder. [2] Lat. *silex*, flint. [3] Greek σίδηρος, iron.

IX. DISEASES OF THE LIVER.

Perihepatitis.

Inflammation of the capsule of the liver, leading to more or less thickening and often to adhesions with adjacent parts, is met with under various circumstances. Its most common causes are—the chronic peritonitis of Bright's disease, chronic alcoholism and syphilis. Localized patches may be produced by pressure from without, as by tight lacing. The changes are usually slight and of but little pathological import.

In some cases, however, especially in cases of chronic peritonitis, the process is more extensive and leads to marked interference with the functions of, and circulation in, the liver. The whole capsule becomes considerably thickened and gradually contracts, thus causing compression of the organ, which assumes a globular form. The portal circulation is often interfered with by the squeezing process, and ascites, with other symptoms of portal obstruction, may result. The liver itself, with the exception of some atrophy and fatty degeneration of its cells, may show no changes; but sometimes it is irregularly intersected, and even divided into lobe-like masses, by bands of fibrous tissue passing inward from the capsule (*centripetal cirrhosis* of Adami).

These conditions have been variously attributed to syphilis, tuberculosis, and alcoholism.

Abscess of the Liver.

1. **Multiple.**—Small multiple abscesses are most frequently due to some inflammatory lesion in connection with the portal system—such as dysentery, appendicitis, ulcerative colitis, typhoid fever, or some other form of ulceration of the gastro-intestinal tract. In these cases the abscesses are due to infective embolism of branches of the portal vein (*suppurative pylephlebitis*). Small abscesses also occur as a manifestation of generalized pyæmia, and are then due to infective embolism of the small branches of the hepatic artery. Suppuration within the bile-ducts (*suppurative cholangitis*) may also give rise to abscesses.

2. **Single.**—Single abscesses may follow injury, either external or internal—in the latter case being due to some foreign body which has perforated the walls of the stomach or duodenum. They may also result from the presence of gall-stones or parasites. In all these cases the abscess is really due to the additional presence of pyogenic organisms. Breaking-down gummata may give rise to extensive abscess-cavities.

The *tropical abscess* is, in three-fourths of the cases, single; and is generally believed to depend upon infection through the portal vein. In a large proportion of the cases it is associated with dysentery. It is commonest in countries near the equator, generally selects the white races, and occurs especially in cases of chronic alcoholism. The Amœba coli is found in some cases, but, as a rule, the B. coli communis and ordinary pyogenic organisms are alone to be found.

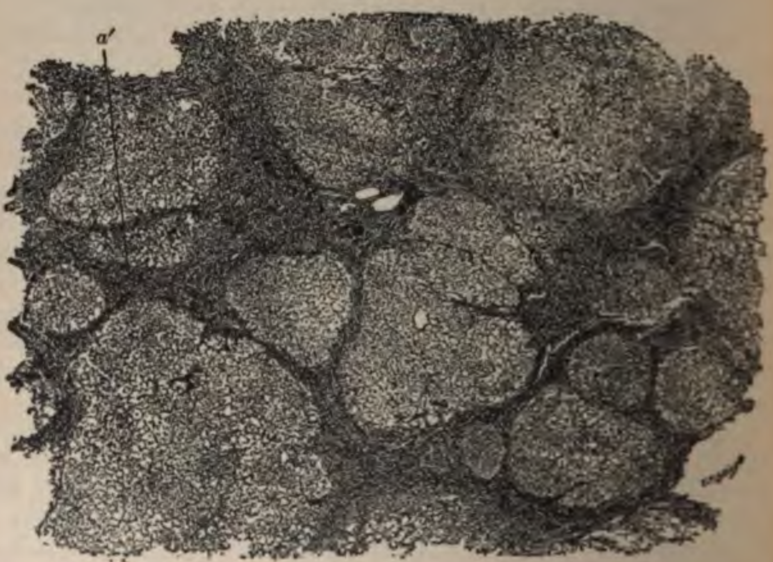
Cirrhosis of the Liver.[1]

Cirrhosis is the term applied to all diseases of the liver mainly characterized by an increase in the connective tissue of the organ.

Although the changes which occur in the diseases included in this definition vary within wide limits, three types may, for convenience of description, be distinguished—(1) *Portal*, (2) *Biliary*, and (3) *Pericellular*.

1. Portal Cirrhosis.—In this form the increase in the connective tissue occurs around the branches of the portal vein, and is, therefore, interlobular in its arrangement. Between many of the lobules, however, no new tissue appears, so that the distribution is exceedingly irregular, and the lobules become grouped into masses of varied size (*multilobular cirrhosis*) (Fig. 290); while the component cells tend to lose their radiating arrangement, and, at the periphery, to undergo fatty degeneration, atrophy, and pigmentation with bile. The new connective tissue is plentifully supplied with bloodvessels from the hepatic artery. Later on it contracts, and forms hard cicatricial tissue, obstructing the portal circulation, and thus giving rise to ascites and to hemorrhage from any part of the gastro-intestinal tract (Fig. 290), as well as press-

Fig. 290.



Portal cirrhosis of the liver. a, a', tracts of fibrous tissue enclosing masses of fatty liver-cells. The distinction between the different lobules and the radiating arrangements of the cells is entirely lost. × 25.

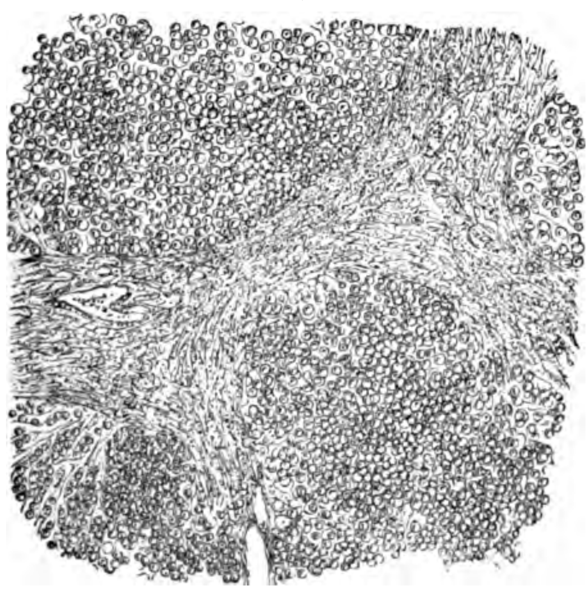
ing on the cells of the liver (Fig. 291). Short columns of cubical cells, usually found in biliary cirrhosis (*vide infra*), are occasionally met with among the new tissue.

Nak d-eye Changes.—In the earlier stages the liver is uniformly

[1] Greek κιῤῥός, yellow.

enlarged, and the edge is rounded and thickened. This increase in size occasionally persists, without any contraction, until the disease ends fatally, but in the large majority of cases the atrophy of the liver-cells and the contraction of the new tissue are followed by some diminution in size. In some cases this may be so extreme—especially in the left lobe—that the liver is less than half its normal weight (*atrophic cirrhosis*), but in at least half the cases the organ at the time of death is larger and heavier than normal. The capsule is thickened and the surface is uneven. When the unevenness is extreme, the liver is termed *hobnailed*—the extent of this depending upon the distribution and contraction of the new tissue and upon the atrophy of the cells. As a rule, the more fatty the liver, the less the contraction. The consistence of the organ is also proportionately increased, and may approximate to that of hard fibrous tissue. Both the irregularity of the surface and the induration are most marked along the anterior edge, especially of the left lobe. On section, the new tissue surrounding the lobes, and in many parts completely replacing them, is visible to the naked eye. This gives to the cut surface a mottled granular appearance, the lobules contrasting with the new interlobular tissue, and often appearing as yellow or orange

FIG. 291.



Cirrhosis of the liver with fatty changes. × 60.

foci in a pink, glistening network. In advanced cases the fibrous tissue is dense and white. In the large majority of cases the spleen is much enlarged, being often double its normal size.

An acute form is occasionally met with, in which the new tissue is abundantly infiltrated with leucocytes (*red atrophic liver*), the disease ending fatally in a few months.

2. Biliary Cirrhosis.—In the typical instances of this comparatively rare form of cirrhosis the new fibrous tissue is evenly distributed between all the lobules (*unilobular cirrhosis*), and even invades the intercellular network. The bile-ducts outside the lobules are large and tortuous, and their external coat is thickened. Scattered through the new tissue—in the majority of cases—are short columns of cubical cells, often arranged in double rows. By some these are regarded as attempts at regeneration on the part of the liver-cells or bile-ducts; by others, as degenerated liver-cells or the surviving remnants of bile-ducts. Adami considers the condition is due to a partial reversion to the original hepatic follicles found in the earliest stages of the development of the liver, and suggests the name "reversionary degeneration."

Naked-eye Changes.—The liver is uniformly, and often enormously, enlarged. Its surface is smooth, its consistence firm, and its color almost olive. On section, the new, evenly distributed tissue can be readily made out. No marked contraction occurs, and, although jaundice is generally present, ascites is extremely rare, and the liver remains large and smooth to the end. Enlargement of the spleen occurs at an early stage.

3. Pericellular Cirrhosis.—In adults, on rare occasions, and frequently in infants dead from congenital syphilis, new connective tissue is found uniformly infiltrating the whole organ, and penetrating everywhere between the degenerating liver-cells (Fig. 225, p. 395). Scattered groups of small round cells suggest the commencement of gummata. The liver is large, and, in most cases, uniform in color.

Other rare forms of cirrhosis are occasionally met with. (1) Arteriosclerosis may, in the liver, as in other organs, lead to slight fibroid changes. (2) Long-continued passive congestion may also produce a development of fibrous tissue around the intralobular veins (p. 202). (3) Cirrhosis may occur with perihepatitis (p. 489), and (4) in a localized form with syphilis (p. 392).

A large number of cases also occur in which the characters of the three types described are so intermingled that many writers deny the utility of the classification adopted, which indeed can only be regarded as representing a provisional arrangement of the facts known.

Boix, under the name of "dyspeptic cirrhosis," describes a uniformly enlarged liver in which the infiltration is interlobular and intralobular, but which does not affect the nutrition of the cells. The disease may disappear under treatment, or, after about ten years, pass into the atrophic form. The spleen is not enlarged, and there is neither jaundice nor ascites. Lancereaux, and many other authorities, recognize a definite variety of cirrhosis, due to malaria; in this form an irregular *intralobular* fibrosis precedes a similar *intercellular* change. A form also occurs in which a large amount of iron-containing pigment is deposited in the liver-cells and in the capillary walls (haemochromatosis), and a few instances in which adenomatous and even carcinomatous growths may be intermingled with the fibrous tissue.

The term *hypertrophic cirrhosis* is not infrequently used as a synonym

of biliary cirrhosis; it is also employed to designate the enlarged stage of portal cirrhosis; and again to denote a form of portal cirrhosis not unlike that which Boix describes, supposed to remain stationary without any contraction throughout its course.

Pathology.—The site and gradual development of *portal cirrhosis* establish a probability that the disease is due to some slowly acting irritant conveyed by the tributaries to the portal vein and, therefore, derived either (1) from the gastro-intestinal tract, or (2) from the spleen.

1. In the great majority of instances the irritant seems to be absorbed from the stomach or intestine. In most cases there is a clear history of chronic alcoholism. The form in which the alcohol is taken does not seem to be of much importance. In one country it is beer; in another, wine; in a third, spirits. But how the alcohol acts, and to what causes are due those cases in which no such antecedents have occurred, are vexed questions. According to the old view, the alcohol itself was the irritant; according to later authorities, the products of fermentation to which the ingestion of alcohol would contribute, and in which acetic acid takes the most prominent part, are believed to be the chief toxic agents; and, according to a third theory, the actual causes of the disease are the toxins of organisms which are enabled to thrive among the tenacious mucus which lines the alimentary tract in those suffering from chronic alcoholic catarrh, or which actually find their way to the portal zone of the lobules of the liver (Adami). Most of the later views are based principally upon experimental evidence. To a large extent this is contradictory, and, indeed, in other ways unsatisfactory, for the periods over which the poisons were administered were much shorter than those usually required to develop chronic cirrhosis in man.

2. Chauffard has suggested that substances derived from the spleen may act as causes of portal cirrhosis. He points out, in addition to various *a priori* considerations, that in several diseases, of which malaria and typhoid fever are typical examples, the spleen acts as a storehouse of infective parasites, and that, in these diseases, secondary phlebitis of the splenic vein and subsequent hepatitis have been found According to Chauffard, the poison is probably derived from the spleen in those cases in which enlargement of this organ appears to precede the cirrhosis of the liver. There is more evidence in favor of a splenic origin of acute hepatitis and of malarial and biliary cirrhosis than of a similar causation of the ordinary atrophic form.

Biliary cirrhosis is generally believed to be of infective origin,* and is most likely due to (1) inflammation of the bile-ducts produced by the elimination of some poisons excreted in the bile—for certain poisons (toluylenediamine) have been shown capable of causing such an inflammation; and more rarely to (2) direct extension from the duodenum up the bile-passages.

From these hypotheses it will be seen that the occurrence of the mixed forms of cirrhosis can be readily explained on the supposition

that the poisons capable of producing each form occur simultaneously in a single case.

It may be asked how far the atrophy of the liver-cells in cirrhosis is due to the immediate effect of the poison and how far to the pressure exerted by the new tissue. Many facts seem to preclude an exclusive reply in either direction. On the one hand, atrophy does not always occur and the new tissue is coarser than, and far in excess of, that required to compensate for the atrophy that has occurred; on the other, the atrophy may commence before any apparent pressure is exerted. There seems to be no good reason why the cause of the cirrhosis should not in many cases, if not in all, have a direct influence upon the nutrition of cells and thus tend to cause their atrophy; and, further, when the new tissue has commenced to contract, it is highly probable that the nutrition of the cells upon which the pressure is exerted will be still further impaired.

Effects of Cirrhosis of the Liver.—The pathological effects which can be directly traced to cirrhosis of the liver are principally disturbances in the portal circulation produced by contraction of the fibrous tissue. The blood thus prevented from traversing the liver, and dammed back in the portal system, causes increase of pressure in this vascular area, which can only be relieved by means of anastomosing channels. The principal anastomoses between the portal and the general venous system are (1) round the anus, by means of the junction between the inferior and upper hemorrhoidal veins; (2) round the umbilicus, by the anastomosis of branches of the veins in the abdominal wall with those of the vein of Sappey in the round ligament of the liver; (3) connections between the mesenteric and retroperitoneal veins; and (4) the anastomoses of the coronary veins of the stomach with the lower œsophageal veins. The enlargement of the anastomosing branches causes (1) hemorrhoids; (2) the *caput Medusæ*, or circle of enlarged vessels visible round the umbilicus; (3) great enlargement of veins beneath the peritoneum throughout the abdominal cavity; and (4) dilatation of the veins at the lower end of the œsophagus. If rupture of these last vessels occur, as not infrequently happens, severe hemorrhage may ensue, the blood passing into the stomach and being subsequently vomited. In other cases the blood is derived from the stomach, in which eroded vessels may be found after death. Bleeding may also occur from the hemorrhoids.

The increase of pressure on the branches of the portal vein is followed by exudation of serous fluid, giving rise within the intestines to a watery condition of their contents and resulting watery motions, and within the peritoneal cavity to ascites. This last is probably aided by—and in many cases principally due to—accompanying chronic peritonitis.

Symptoms arising from interference with the functions of the liver are difficult to recognize in these cases. In some forms of intense cirrhosis, however, there occur fever, jaundice, a hemorrhagic tend-

ency, delirium and coma—the whole constituting a picture closely resembling that seen in acute yellow atrophy of the liver.

Acute Yellow Atrophy.

This rare disease of the liver is characterized by a rapid diminution in the size of the organ, accompanied by the degeneration and subsequent destruction of the hepatic cells. Hemorrhages from any part, jaundice, and delirium are among the principal manifestations of the disease. The malady is commonest in women, and is, in this sex, generally associated with pregnancy. The liver may, in the course of a few days, be reduced to less than half its normal bulk, being especially diminished in thickness. It is soft and flabby in consistence, bloodless, and of a mottled yellowish-red color. A section through the organ shows numerous intermingled patches, dark red and bright orange in color; in the lighter parts the lobules are generally indistinguishable. When examined microscopically, it is found that the protoplasm of the liver-cells is completely replaced by granular débris, fat-granules, and pigment, and that many of the cells have absolutely disappeared. In the earlier stages, the small bile-ducts are filled with débris. Tyrosin and leucin have been found in the disintegrated liver-tissue and in the hepatic veins. The appearance of these substances in the urine is characteristic of the disease. Branched tube-like collections of cubical cells, suggestive of bile-ducts, are frequently seen among the surviving stroma (p. 492). The kidney and spleen undergo very similar changes. The pathology of this disease is exceedingly obscure. It is generally regarded as an acute degeneration, depending on some unknown toxic cause derived from intestine or spleen. The jaundice is probably due to the blocking of the smallest ducts with the products of degeneration. The existence of leucin and tyrosin in the urine is probably due to the abolition of the functions of the liver, one of which may consist in converting into urea certain intermediary products of proteid metabolism.

A somewhat similar condition occurs in acute phosphorus-poisoning; although in this case the liver is enlarged, and the patches of yellow and red are never so distinct.

For syphilitic disease of the liver, see page 377. Compare also Fig. 41, showing secondary malignant disease of this organ.

Gall-stones.

Gall-stones are concretions, generally formed during late adult life, either in the hepatic ducts or in the gall-bladder. In size they range from mere gritty particles to masses as large as pigeon eggs. The number found in a single gall-bladder varies from one stone to several thousands. In color they vary from a pearly white to a greenish black. Occasionally, when distinctly crystalline to the naked eye, they may be pale yellowish green and semi-transparent. As a rule, they can be easily crushed between the fingers, and are so light that when dried they float

on water. They are generally quadrilateral or prismatic in shape, with some sides flattered, owing to mutual pressure while the stones are still soft. These flattened surfaces are termed *facets*. Single stones are never faceted; neither are very small ones, as they can roll easily on one another without exerting any marked pressure. Facets occur chiefly in calculi of medium size, if more than two or three be present: they are not due to erosion after stones are formed, as, on section, the same laminæ can be traced all round the stone (Fig. 292).

Fig. 292.

Gall-stones. *a*, *b*, are gall-stones formed in each case singly: *a* is composed of almost pure cholesterin; *b* consists of bilirubin-calcium and cholesterin; *c*, *d*, *e*, *f* are examples of various forms occurring in different cases, and in each instance in large numbers; *g*, ten similar stones were removed from a gall-bladder, the white portions of the outer layer are composed of cholesterin, the dark edges of bilirubin-calcium; *h* is a magnified view of one of the other stones from the same case, showing the origin of the central cavity with its crystallised contents and the various added layers.

When carefully examined, a gall-stone is found to consist of a soft nucleus and a harder laminated crust. Within the nucleus there is often a cavity. Both nucleus and crust may be of the same composition. Cholesterin and bilirubin-calcium are the most important constituents. Crystalline stones consist mainly of the former, and the largest calculi are generally made up of pure cholesterin; but a stone consisting mostly of this substance is by no means always crystalline.

Pathology.—It was formerly supposed that foreign bodies acted as the nuclei of gall-stones, and that cholesterin and other biliary constituents were deposited from concentrated, or otherwise altered, bile. It has, however, been shown experimentally that the introduction of foreign bodies into the gall-bladders of dogs does not cause any such precipitation, and that if gall-stones themselves are introduced into a normal gall-bladder they dissolve and disappear. It has also been shown that an important source of cholesterin is an extensive destruction of the lining epithelium, and that the precipitation of bilirubin-calcium is induced

by the presence of albumin in the bile. From these and other facts it is believed that a mildly infective catarrh of the lining membrane of the ducts is the first stage in the production of calculi. Such catarrh can be produced experimentally by the introduction into the gall-bladder of attenuated cultures of the colon-bacillus, of the typhoid bacillus, and of the ordinary pyogenic cocci. The catarrh is accompanied by the desquamation and disintegration of the epithelium, and by the exudation of albuminous fluid. Bilirubin-calcium next separates out, especially from stagnant bile, and, with the desquamated epithelium, forms a nucleus round which a shell of more bilirubin-calcium is deposited. As the epithelium disappears, a central cavity is left which, later on, is generally filled up with cholesterin derived from the disintegrated epithelium. Further layers are subsequently deposited, but always together with albuminous matter, for, if the salts be dissolved out artificially, a complete organic framework remains.

Effects.—A gall-stone may block the duct in which it is formed, or to which it may be carried, and, in that way, give rise to obstructive jaundice (p. 81). By the irritation of its presence it may produce inflammation and ulceration of the wall of the duct or bladder, and, if pyogenic organisms are present, give rise to an abscess. From the gall-bladder, or from the ducts, calculi may escape into the duodenum. In some instances a stone in the gall-bladder, or in the common duct near its entrance into the intestine, may produce inflammatory adhesions of the neighboring parts and subsequent ulceration. By this means a stone too large to pass through the orifice of the duct is enabled to make its way into the bowel, and lower down, where the lumen of the intestine is smallest, to give rise even to intestinal obstruction. Carcinoma may arise as the result of the irritation caused by gall-stones.

X. DISEASES OF THE PANCREAS.

Diseases of the pancreas arise for the most part from the entrance of pathogenic organisms into its ducts. In cases of invasion by very virulent germs the whole organ, or large parts of it, may undergo **necrosis**, or an acute interstitial inflammation may ensue. Less virulent infection results in a process of chronic **fibrosis**. Two varieties of this have been distinguished by Opie: (1) *Interlobular* fibrosis, in which the fibrous tissue is irregularly distributed between the lobules of the gland; and (2) an *Interacinar* form, in which it is uniformly distributed, passing between the individual acini. The pancreas is generally shrunken, and its cells atrophied, in both these conditions; but occasionally fibrosis may be associated with great enlargement of the gland. The resemblance of these fibrotic conditions to the different varieties of cirrhosis of the liver is very marked.

The pancreas and the tissues round it are often the seats of **hemorrhage**, the cause of which is not understood. **Calculi** may also form in its ducts; and these, by blocking the ducts, or by obstructing

the opening of the papilla of Vater into the duodenum, and thus causing the regurgitation of bile into the pancreas, may give rise to fibrosis of the gland or to the formation of **cysts.** **Fatty degeneration** is liable to occur in this organ, and **atrophy** of the cells is also described; the latter is often accompanied by some secondary fibrosis. **Carcinoma** as a primary disease is not very uncommon in the pancreas. The questions of the relation of the pancreas to fat-necrosis and to diabetes mellitus are discussed elsewhere (see Chap. XI.).

XI. DISEASES OF THE KIDNEY.

Suppurative Nephritis.

Suppurative nephritis results from the transmission to the kidneys of pyogenic bacteria from some primary focus. It may occur (1) as one of the lesions in pyæmia; or (2) may be associated with some pyogenic inflammation of the lower urinary passages. In pyæmia, the infective organisms are transmitted by the bloodvessels. In the other cases they reach the kidney by direct infection from the lower urinary passages.

As, however, regurgitation of urine from the bladder into the ureter does not occur, bacteria often thrive in the former organ for considerable periods without infecting the ureter and kidney. When infection does occur it is sometimes due to the growth of organisms in ropy mucus,

FIG. 293.

Suppurative nephritis. Showing crowds of micrococci along the tubules. Almost all nuclei in their vicinity have disappeared. The tissues seem to have undergone coagulation necrosis. × 90.

lying as a cord in the opening of an inflamed ureter; but is more frequently the result of the transmission of bacteria by the lymphatics of the ureters.

1. The abscesses met with in the kidney, as the result of pyæmia, are confined principally to the cortex, and resemble pyæmic abscesses in other organs. They are usually multiple, and are often surrounded by a narrow zone of red hyperæmic tissue. They usually originate around the glomeruli, in the capillary tufts of which the organisms have been arrested. Their size varies from a mere point to that of a filbert.

Their characters have been already described and illustrated (pp. 170 and 342).

2. When the suppurative inflammation is due to infection from the lower urinary passages (*acute surgical kidney, acute consecutive nephritis*), the pelvis of the kidney is generally acutely inflamed, and many of the convoluted tubes are crammed with micrococci. These seem to ascend from the pelvis along the tubes, distending them, and giving rise, along their line of growth, to cloudy swelling, coagulation-necrosis, and either suppuration or a diffuse infiltration of the interstitial tissue with leucocytes (Fig. 293). The urine in the pelvis of such kidneys usually contains pyogenic organisms.

The cortex of such a kidney is thickened, soft, and pale as compared with the deep-red pyramids; its consistence, however, will vary with the presence or absence of chronic interstitial changes. The capsule strips easily, often tearing the substance a little, and exposing on the surface groups of yellow spots. These yellow dots are never larger than a split pea; each is surrounded by a red zone, and many of them contain a drop of pus. On section, yellow streaks are often seen extending from the superficial lesions into the cortex; others exist in the pyramids.

Hydronephrosis.

Chronic changes in the kidney result from diseases causing obstruction in the lower urinary passages. They occur in association with renal and vesical calculi, obstructed ureter, urethral stricture, and enlargement of the prostate.

When the flow of urine from the ureter into the bladder is permanently impaired by any form of obstruction, the increased pressure due to the force of secretion, aided by that of gravity, seems to expend itself in gradually dilating the ureter, the pelvis, and the pyramids, and, finally, the tubules even to their closed ends (*hydronephrosis*), leading to atrophy of the tubular epithelium and increase and induration of the interstitial tissue. When the obstruction to the outflow is confined to *one* kidney, that organ is alone affected.

The overgrowth of the interstitial tissue is exceedingly irregular in distribution and amount. It occurs both in the pyramids and cortex (*chronic consecutive nephritis*). The tubules are in some parts found blocked with epithelium, whilst in others they are wasted or obliterated. Owing to these changes, the kidneys are somewhat enlarged, the capsule is slightly adherent the cut surface is paler than natural, and the consistence of the organs is abnormally tough. The walls of the small arteries are not thickened. As the process advances, the pyramidal portions gradually become absorbed, the absorption commencing at the papillæ and extending, until ultimately not only the pyramids, but also the thickened cortex may disappear, and the kidney be converted into a large cyst divided into sacculi by fibrous septa (hydronephrosis). If, on the other hand, the urinary obstruction be removed, the processes of inflammation and absorption may cease, and the indurated kidney will then become contracted.

Bradford has shown that if hydronephrosis be artificially induced, atrophy of the tubules and shrinking of the remaining epithelium occur even when the obstruction is removed and the kidney completely drained.

Parenchymatous Nephritis.

Parenchymatous nephritis includes those forms of inflammation of the kidneys in which the secreting tissues are primarily affected. The damage is caused by substances reaching the kidneys by way of the blood-stream. While in ordinary metabolism the waste products escape by the glomeruli or are excreted by the tubular epithelium, without any injury to the structures concerned, the substances giving rise to parenchymatous nephritis cause damage to the tissues in the process of their excretion, and in this way lead to changes in the glomeruli or in the renal tubules, or in both of these. These changes, supplemented by more or less inflammatory reaction, give rise to the morbid appearances characteristic of the disease.

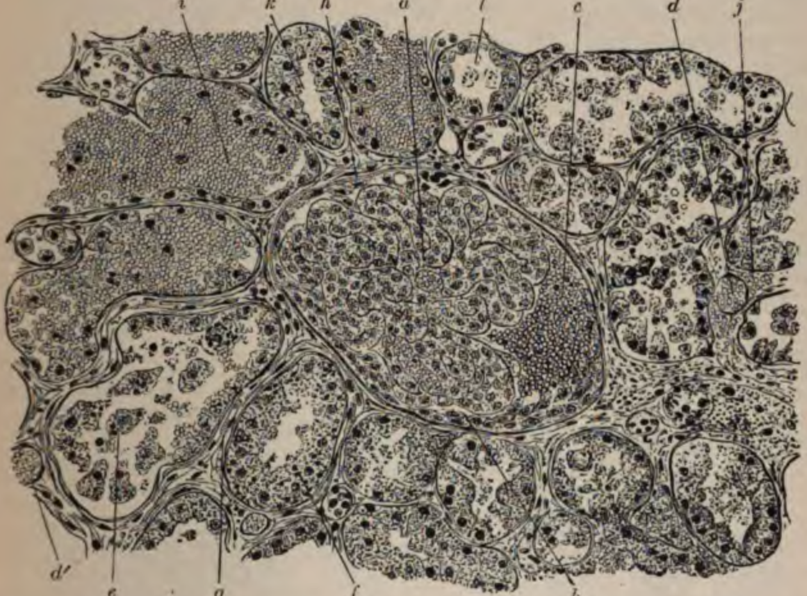
The actual substances producing these results are, to a limited extent, known. Thus (1) cantharides, turpentine, oxalic acid, compounds of phosphorus, and salts of mercury and arsenic are well-ascertained causes. (2) Bacterial toxins and the products of the disordered metabolism occurring in diseases, the bacterial origin of which cannot yet be positively affirmed, form another important group; including among others, diphtheria, scarlatina, typhoid fever, acute pneumonia, and septicæmia. In some of these the actual organisms reach the kidneys and produce local lesions there. (3) Other diseases, such as gout and diabetes, accompanied by grave disorders of metabolism, also act as causes of parenchymatous nephritis. (4) Many instances of the disease occur apart from the foregoing causes. Some cases occur in persons suffering from alcoholic excess, prolonged exposure to cold and wet, extreme exhaustion, or any combination of these. To these cases no definite causation can be assigned, but in most of them the existence of disordered metabolism is highly probable.

The altered composition of the urine furnishes the first evidence of the damage to the kidneys. The injured glomeruli permit the escape of serum-albumin, serum-globulin, and, in severe cases, of blood. The necrosed or degenerating tubular epithelium becomes entangled in the blood or albuminous fluid thus secreted, and forms moulds of the renal tubules. These block the tubules and prevent the escape of urine, while portions of them appear in that secretion as cylindrical casts. The amount of urine and of urea secreted is diminished, and œdema of the loose connective tissue occurs. That these results are not due solely to the diminished amount of renal tissue available for secretion is probable from the experiments of Bradford, who has shown that the effect of excising large portions (two-thirds of the total amount) of kidney-substance is to increase the quantity of urine and of excreted urea, although at the same time the amount of urea produced in the body is so great that it accumulates in the blood. This result may be

due, as Bradford hints, to the cessation of the action of an internal secretion normally supplied by the kidney.

Varieties.—Parenchymatous nephritis is generally divided into two varieties, *glomerular nephritis* and *tubular nephritis*. In the glomerular variety the glomeruli are the principal seats of the disease and may be the only parts affected. In the tubular variety the tubules are affected equally with, and sometimes even more than, the glomeruli. Tubular nephritis is subdivided into acute and chronic varieties.

Fig. 294.



Acute tubular nephritis. *a*, capillary tufts of glomerulus, containing a large number of leucocytes; *b*, proliferated and desquamated cells of capsule; *c*, extravasated red blood-corpuscles; *d*, *d'*, capillary bloodvessels; *e*, degenerated epithelial cells detached from wall of tubule; *f*, granular degeneration of tubular epithelium; *g*, thickened intertubular tissue; *h*, capsular epithelium; *i*, extravasated blood-corpuscles in tubule; *j*, extravasated blood in intertubular tissue; *k*, slightly degenerated epithelium; *l*, one of many tubules presenting various degrees of degeneration or necrosis of their epithelium. × 225.

Morbid Anatomy. (1) *Naked Eye.*—In the *glomerular* form the naked-eye appearances may be absolutely normal, though occasionally the glomeruli stand out as sharply defined gray points. In the *tubular* form the kidneys are always larger than normal and may be increased to twice their natural size. The enlargement is due partly to hyperæmia, partly to distention of the tubules, and partly, in some cases, to œdema of the intertubular tissue. The capsule separates readily, exposing a smooth and often hyperæmic surface. The consistence is diminished, and the substance soft and friable. On making a longi-

tudinal section, the increase in the size of the organ is seen to be mainly due to swelling of the cortical portion. This may be pale or dark, but is generally mottled—reddish patches being mingled with those of an opaque white or buff color. The differences in color depend upon the proportion which the hyperæmia and hemorrhage, on the one hand, bear to the accumulation of degenerated tubular epithelium, on the other. In the earliest stages of the most acute forms of the disease the cortex is generally redder than natural, but it soon becomes pale and opaque. This is owing to the progressive necrosis, degeneration, and accumulation of the tubular epithelium. When hemorrhage has occurred into Bowman's capsule, the Malpighian bodies stand out as prominent red points. The pyramids in the medulla are of a deep-red color, contrasting strongly with the pale, opaque cortex.

(2) *Microscopic.*—In the *glomerular* form, of which the most typical instances may be seen in scarlatina, the changes are often confined to the Malpighian bodies. The intracapsular spaces are found to contain a number of new and, as a rule, degenerated cells. Some of these are derived from the cells which once covered the vascular tuft and lined the capsule, which may have thus lost all its epithelium. Mixed with these may be a few leucocytes and possibly a few cells derived from the endothelium of the capillaries. Some of the capillary loops are distended and contain an unusually large proportion of leucocytes

FIG. 295.

Tubular nephritis. The earlier stage of the process. Showing the swelling of the tubular epithelium, and some exudation-products in the urine-tubes. In some of the tubes the epithelium has fallen out during the preparation of the section. × 200.

which not infrequently show signs of degeneration, while the endothelial cells are much swollen and often proliferated. The new cells are sometimes accompanied by so much albuminous exudation that the vascular tuft is compressed and the circulation through it thereby impeded. In some cases the intima of the minute arteries, especially of those supplying

the glomeruli, undergoes hyaline degeneration with consequent narrowing of the lumen of the affected vessels. The muscular cells of the smaller arteries may also be thickened and the nuclei increased. Cloudy swelling of the epithelium in the convoluted tubes may be superadded.

In the most acute cases a cellular infiltration of the intertubular connective tissue may occur, with marked degeneration of the epithelium and a crowding of the tubes with leucocytes. The cellular infiltration is especially prone to occur in the neighborhood of the interlobular and stellate veins; but these cases closely approximate to the tubular variety.

In *tubular* nephritis the glomeruli undergo much the same changes as in the previous variety. Tubular nephritis is, however, generally more intense; the hyperæmia is therefore more marked, and hemorrhage into Bowman's capsule and the tubules is more frequent (Fig. 294). In the kidneys of persons dying in an early stage of the disease large numbers of red corpuscles may accordingly be seen in the Malpighian bodies, pushing to one side the vascular tufts, as well as in the tubules, which may be distended.

The tubules show marked changes. These are generally most prominent in the convoluted tubes, although they may be almost as advanced in the straight tubes. In the most acute cases many of the epithelial cells are necrosed and their nuclei remain unstained (Fig. 294). More frequently, especially when the onset of the disease is less intense, the cells undergo cloudy swelling and fatty degeneration (Fig. 295). The dead and damaged epithelium becomes detached and collects in the tubules.

The coagulable exudation, which now enters the tubules from the Malpighian bodies, forms the basis of the numerous *casts* which block the tubules and give rise to a scanty deposit in the urine. The basis or matrix of these casts is transparent, and, when no other material is imbedded in them, they are known as *hyaline casts*. Casts containing blood, desquamated epithelium, leucocytes, granular débris, or fatty molecules, are named according to their respective contents (Fig. 296).

FIG. 296.

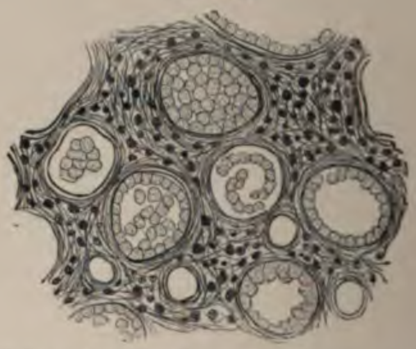
Tubular nephritis—a single tubule. Showing the accummulation within the tube. In the few epithelial cells which have escaped, the granular condition of the protoplasm is seen. × 200.

Later Changes.—At this stage the changes already described may subside, and, with the exception of some desquamation of damaged epithelium, no further degenerative changes take place in the kidneys. Many of the surviving epithelial cells proliferate, but in all probability the repair is never absolutely complete. Thus the organs return to about their normal condition, although, for some weeks longer, casts and albumin may be passed in the urine.

In other cases the disease progresses, and, although the hyperæmia is less marked, the degeneration of the tubular epithelium continues. In these cases, as well as in others in which the onset has been far less acute, the desquamated epithelial cells which come away with the urine, instead of presenting a swollen granular appearance, as in the earlier stages, constantly contain molecules of fat. The amount of fat thus passed gradually increases as the degeneration proceeds, until ultimately no recognizable cells can be found, and the fat appears as free globules in the tube-casts.

This prolonged fatty degeneration of the epithelium is attended by corresponding changes in the appearance of the kidneys. No hyperæmia

Fig. 297.



Tubular nephritis (large white kidney). Duration of disease, six months. Kidneys, large; capsules, non-adherent; surface, smooth; tissue, soft. Showing, in addition to the intra-tubular change, the cellular infiltration of the intertubular connective tissue. × 20.

is noticeable. The enlarged cortex presents a more uniformly yellowish-white tinge, studded with minute yellowish streaks owing to the presence of fat in the tubes. Even at this stage repair may occur and ultimately recovery ensue.

When the inflammatory process is of still longer duration, or when the kidneys are the seats of repeated attacks of subacute inflammation, permanent changes occur and the intertubular connective tissue becomes involved (*large white kidney*) (Fig. 297). The tubular epithelium shows little tendency to proliferate, and considerable portions of the tubules may be completely denuded. The intertubular tissue develops into a loose fibrous structure which, together with the atrophy of the damaged glomeruli and denuded tubules, leads to much diminution in size, especially of the cortex, and to slight irregularity of surface (*small white kidney*). The new tissue is, however, more uniformly distributed and the contraction less marked than in the condition known as *granular kidney* (p. 505). The surface is pale, mottled with red. In other cases death ensues before any marked atrophy has taken place, while the tubules are distended or blocked by the degenerated products, and the intertubular tissue is loose and œdematous (*large*

white kidney). Attacks of subacute inflammation not infrequently occur in the course of the more chronic cases of parenchymatous nephritis.

Chronic Interstitial Nephritis.

It has already been shown that an increase in the interstitial tissue of the kidney occurs in the more advanced stages of tubular (p. 504),

FIG. 298.

Large white kidney. *a*, smooth surface with venules; *b*, pale and thickened cortex; *d*, dark pyramids. Natural size.

and of chronic consecutive nephritis (p. 499). But this change is especially prominent in that most chronic of all varieties of disease of the kidneys known as *contracted kidney*, *granular kidney*, *cirrhosis of the kidney*, *gouty kidney*, or *chronic interstitial nephritis*. In this disease the development of fibrous tissue is associated with atrophy of the glomeruli and tubules, and changes in the walls of the arteries.

Clinically, the disease is characterized by an insidious onset, increased arterial tension, polyuria, hypertrophy of the left ventricle of the heart, and degenerative changes in other tissues. Albuminuria, if present, is slight, and dropsy is absent, except as a result of cardiac failure. The disease is most frequent in the declining period of life. It is often associated with gout, chronic lead-poisoning, over-indulgence in alcohol, and, perhaps more often than is generally believed, with syphilis.

Morbid Anatomy.—In a well-marked case (Fig. 299) the kidney is much diminished in size. Its capsule is thick and very adherent;

Fig. 299.

Granular contracted kidney. *a*, rough, granular surface; *b*, dark, narrow cortex; c, c^1, c^2, cysts; *d*, pyramids. Natural size.

it cannot be removed without tearing the substance. The surface is coarsely granular and of a reddish-gray tint. On section, the color of both pyramids and cortex is seen to resemble closely that of the surface, the distinction between cortex and pyramid being often by no means clear. The cortex is, however, more mottled, and small patches can sometimes be made out corresponding to the depressions between the minute nodules on the surface (Fig. 300). Moreover, it is much narrower and tougher than normal; and small cysts are often found, especially on its surface. Calcareous deposits may occasionally be seen

as white streaks among the tubes of the pyramids. In the earlier stages of the disease all those changes will be much less marked.

FIG. 300.

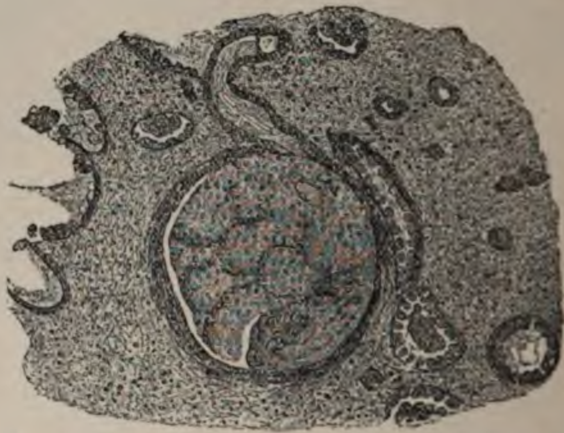
Granular contracted kidney. *a*, perirenal fat; *b*, thickened capsule; *c*, wedged-shaped mass of fibrous tissue corresponding to depression between nodules on surface; *d*, *e*, glomeruli in different stages of atrophy; *f*, *j*, renal tubules; *g*, *h*, fibrous strands extending from thickened capsule into cortex; *k*, glomerulus beginning to atrophy. × 35.

If a section cut through one of the depressions just mentioned be examined *microscopically*, it will be found to contain a number of shrunken Malpighian bodies and a few atrophied or distended tubes imbedded in a mass of fibrous tissue (Fig. 301). Bowman's capsule is, in each case, more or less thickened.

The rest of the cortex is by no means uniformly affected. In many parts the tubes are diminished in size or completely obliterated; in

others they are dilated and filled with degenerated epithelial products (Fig. 301). Their walls are often thickened. The intertubular tissue is increased throughout, but by no means uniformly, so that not infrequently the cortex may be traversed by irregularly disposed fibrous

Fig. 301.



Granular contracted kidney. An advanced stage of the process, showing the overgrowth of interstitial tissue, the thickening of Bowman's capsule, and the atrophy of the tubules. × 120.

bands. The new tissue may be largely cellular or densely fibroid. The atrophy of the Malpighian bodies and adjoining tubes may be out of proportion to the amount of interstitial overgrowth (Fig. 300).

Fig. 302.

Arteries from case of advanced granular contracted kidney. *a*, longitudinal section, showing the great thickening of the circular muscular coat, also of the outer fibrous coat, and the internal connective-tissue layer; *b*, transverse section of another vessel less diseased. Here is seen the thickening of the circular muscular and external fibrous coat. × 200.

The walls of the interlobular arteries and the smaller cortical vessels are much thickened. Sometimes the external coat is principally involved, and appears to be continuous with the new intertubular tissue. Sometimes the middle coat is thickened, as in the specimen from which the accompanying illustration was taken (Fig. 302). Johnson attributed

this to hypertrophy of the circular muscular fibres. Recent observers emphasize the frequency with which the intima is involved: the endarteritis thus produced most closely resembles that form already described as syphilitic (p. 392). The changes in the arteries are by no means limited to those of the kidneys, but are found in the arteries of almost any part of the body.

In some cases there is marked thickening of the arterial walls and atrophy of the glomeruli and tubules, but no new fibrous tissue (*arteriosclerotic kidney*—Ziegler).

Pathology.—The relationship which these changes bear to one another is but imperfectly known. It is by no means certain that this relationship is in all cases the same. Two explanations have been suggested. According to the first and older view, the changes are due to the action of some unknown irritant, conveyed by the blood to the kidneys, which causes proliferation of the connective tissue in the immediate neighborhood of the vessels. According to this explanation, a granular kidney is analogous to a cirrhotic liver. The thickening in the vessels and the increase in the intertubular tissue are the earliest, and practically simultaneous, changes; while the atrophy of the secreting tissue is due to the results of the contraction of the chronic inflammatory tissue.

According to a more recent and more generally accepted view, this order of events is reversed. The secreting tissues, from overwork and from the premature exhaustion of their inherited vital capacity, are unable to utilize such nourishment as is supplied by the blood, which in most, if not all, cases is defective or even deleterious owing to arteriosclerosis, or anæmia, or some toxic blood-state. The secreting tissues, constituting the most highly organized part of the kidney, will have the greatest difficulty in assimilating nourishment under abnormal conditions, and, in any general interference with nutrition will, therefore, be those most likely to suffer. Thus, the shrinking of the glomeruli and tubules forms the initial change (Fig. 300). The changes in the bloodvessels and the increase in the interstitial tissue follow. The latter is, in many cases, more apparent than real, being partly due to mere condensation of the previously existing, but more widely separated, tissue. As was noted in regard to the cirrhotic liver (p. 494), so in the case of the granular kidney, it is possible that the same irritant may cause both degeneration of the secreting cells and also proliferation of the connective tissue.

The subsequent contraction of the new tissue necessarily constricts many tubules. The arrest of the flow of urine, in those supplied by glomeruli whose vessels are still permeable will lead to the formation of small retention-cysts, such as have been previously described.

Sometimes, as stated above, the arterial changes are more marked than the atrophy of the glomeruli and tubules. In these cases the endarteritis, by diminishing the lumen and hence the blood-supply, is possibly responsible for the production of the atrophy (*arteriosclerotic*

kidney). Cohnheim held that the supply of blood to the kidneys varied with the amount which it contains of those substances which the kidneys normally eliminate (*e. g.*, urea). Atrophy of part of the excretory apparatus, by throwing more work on the remainder, might not improbably lead to an increase in the percentage of these substances in the blood. Now, the only way in which the more free elimination of these by the kidneys can be brought about is by the increased action of the left ventricle and a simultaneous increase in the resistance in the arterioles of other parts. By this means a larger amount of blood may be supplied to the kidneys, and their excretory functions thereby assisted. It is suggested that this may result from some reflex mechanism. It is possible, however, that toxic substances which should be eliminated by the kidneys cause spasm of the arterioles, and thus raise the pressure in the arteries. The heart has to work harder to overcome this, and hypertrophy of the left ventricle results. This increased cardiac action still further raises the tension in the vessels. Thickening of the vessels results from the continued action of the etiological factors (p. 464) and from the increased strain produced by the hypertrophy of the heart.

The enlargement of the left ventricle is a true hypertrophy, though it is often combined with a small amount of chronic myocarditis.

Effects.—The phenomena of *uræmia*, resulting from defective action of the kidneys, are discussed in the next chapter.

In some forms of renal disease excretion of salts is defective, and the characteristic œdema has been attributed to accumulation of sodium chloride in the tissues. The excretion of water is, however, also defective in acute affections. The appearance of albumin in the urine is due to damage to the renal epithelium, which normally prevents the passage of this substance from the blood.

Urinary Calculi.

Any of the passages or cavities of the urinary tract lined with epithelium may be the seat of hard concretions of mineral matter, known as calculi. The two principal seats of these bodies are (1) *the pelvis and calices of the kidney* and (2) *the urinary bladder*—positions in which stagnation of urine is most liable to occur.

In *size* calculi vary from mere particles of grit to masses more than an inch in diameter. When calculi are small, they are frequently multiple; when large, they are usually single. Small calculi are often irregular in *shape*, though they tend to assume gradually the special forms obtaining among the larger varieties. The shape of a large calculus varies with the situation in which it is formed. Thus a large stone in the pelvis of the kidney generally possesses irregular projections, corresponding to the openings of the calices (*coral calculi*); while a calculus in the bladder is generally round or oval. On *section*, a calculus is seen to be made up of a central nucleus and a crust composed of a large number of thin concentric laminæ. The color, hardness, surface,

and sectional appearance of a calculus depend almost entirely upon its composition (Fig. 303).

The three most important groups of substances found in calculi are (1) uric acid and its salts, (2) calcic oxalate, and (3) calcic and ammonio-

FIG. 303.

Vesical calculus. The pale external zone consists of calcic phosphate. Immediately internal to this is an irregular layer of calcic oxalate. Within this are a number of thin layers of calcic oxalate and mixed phosphates. The innermost ring consists of calcic oxalate surrounding a nucleus of urate of ammonium. Natural size.

magnesic phosphates; although other substances, such as calcic carbonate and cystine, are occasionally met with.

(1) The uric acid calculus is of a dirty fawn color: its consistence is hard, and its surface smooth or slightly granular. (2) The calcic-oxalate calculus is dull grayish-brown, intensely hard, and coarsely granular. (3) A phosphatic calculus is white, friable, and smooth.

The three types are not infrequently combined in the same calculus, giving rise to laminæ with corresponding differences in appearance and consistency. Thus, a calculus may contain uric acid in the centre and oxalate of lime in the crust, or may consist of a nucleus of oxalate of lime with laminæ of calcic phosphate and of ammonic urate around it.

In addition to the mineral constituents, a urinary calculus contains a complete organic framework infiltrating the whole calculus and supporting and cementing the mineral particles.

Etiology.—Although the conditions giving rise to the formation of calculi are but imperfectly understood, it may be stated that they depend partly upon general causes and partly upon local changes. Heredity, age, climate (cold), and diet (nitrogenous) have each a marked influence in the production of certain calculi; while such local changes as may lead to damage of the epithelial lining of the urinary passages, and to stagnation of the urine are in all probability still more important causes. Calculi due to the former causes (uric acid, calcium oxalate) might be described as *primary*, those due to the latter (phosphates) as *secondary* (Daniel). But the conditions are frequently combined. Tuffier showed that dogs fed on oxamide developed calculi, and

that particles of oxamide could be traced in both the desquamated and the still living epithelium at the sites of the calculi. It seems, therefore, probable that degenerated epithelium may have an influence in producing calculi somewhat analogous to that possessed by the epithelium of the biliary passages in the production of gall-stones, and that the organic matter found in the calculi is derived from the destroyed epithelium. This is the more probable from the fact that while phosphatic concretions may form around foreign bodies introduced into the bladder, this does not happen until the irritation of the foreign body has produced a recognizable amount of inflammation. Changes in the reaction of the urine may also aid in the precipitation of mineral matter. Thus uric acid and its salts tend to be precipitated when the acidity of the urine is abnormally increased, while calcic and ammonio-magnesic phosphates are deposited in precisely the opposite circumstances. When excess of carbonate of lime exists with oxalic acid in acid urine, oxalate of lime calculi are most likely to be formed. It is also probable, in view of Tuffier's results, that the general causes may lead to definite local changes in the renal tissue, dependent on the nature and concentration of the substances conveyed to the kidneys, and that the precise result may be modified by the antecedent and subsequent local changes. Thus, in one kidney was found a calculus with a uric acid nucleus and a crust of calcic phosphate, while in the opposite kidney was a stone with a similar nucleus but with a calcic oxalate crust.

Some observers have attached considerable importance to the rôle of bacteria in producing calculi, but the action of these is certainly not essential. It is not improbably responsible for the deposit of phosphates which occurs secondarily.

Effects.—**Urinary** calculi give rise to irritation of the lining wall of the cavity in which they lie, and not infrequently obstruct the outflow of urine.

Renal calculi lead to atrophy of the glandular substance, hydronephrosis, and concomitant fibrosis of the kidney. Blood is frequently present in the urine, and desquamated epithelial cells may be found. If infection with pyogenic organisms occur, a purulent inflammation of the pelvis (*suppurative pyelitis*) may ensue, sometimes involving the kidney-substance (*pyelonephritis*) or producing a purulent hydronephrosis (*pyonephrosis*). Inflammation of the tissue around the kidney (*perinephritis*) is a still less usual result. The frequent occurrence of calculi with malignant disease must not be forgotten, although the nature of the association is not understood.

Vesical calculi lead to changes in the bladder of a similar nature as well as, in some cases, to hypertrophy of the muscular coat. They give rise to severe pain and to hæmaturia.

XII. DISEASES OF THE OVARY.

The ovary is very commonly the seat of **inflammation** (*oöphoritis*). In some cases this may start as a local or general peritonitis (*perioöphoritis*), involving chiefly the surface-epithelium and cortex of the organ. The tendency of such a condition is, however, to spread inward and produce a general oöphoritis. Inflammation of the ovary may end in resolution, or in fibrosis (*sclerocystic disease*) and atrophy with loss of function; or it may result in suppuration or hæmatoma. The effused blood in the latter case may undergo calcification. The commonest causes of suppurative inflammation (*ovarian abscess*) are puerperal fever and gonorrhœa; a less frequent cause is tuberculosis. In a gonorrhœal abscess the diplococcus of Neisser is never found, but streptococci and staphylococci abound, pointing to a secondary or mixed infection.

Tubercular oöphoritis is nearly always a secondary infection, resulting from a tubercular peritonitis or from primary disease of the Fallopian tube. Primary tuberculosis of the ovary is very rare.

In chronic oöphoritis **blood-cysts** are not uncommon, and in rare instances they may undergo calcification. These cysts and the calcareous bodies so formed are almost invariably associated with imperfect development or retrogression of the corpus luteum.

Owing to its freedom of movement and to its special functions, the disposition of the ovary to the formation of tumors exceeds that of almost any other organ of the body. **New growths** arise both from the parenchyma and from the stroma of the ovary. The parenchyma consists principally of the epithelium lining the Graafian follicles, but also, to some extent, of germinal epithelium. Both these elements are confined to that part of the gland which is called the oöphoron, and which roughly corresponds with the peripheral zone: they are absent from the paroöphoron or hilum of the ovary. Of parenchymatous growths the most common is *cystic adenoma*; *carcinoma*, *dermoid cysts*, and *teratomata* also occur; the last two growths arise from the ovum, and are therefore termed "ovigenous." Of tumors which arise in the stroma there are three groups—*fibromata*, *sarcomata*, and *endotheliomata*; these last arise from the endothelium or from the tunica adventitia of the bloodvessels and lymphatics.

The ovary is the seat of three types of **cysts**: (1) *distention cysts*, including hydrops folliculorum and cysts of the corpus luteum; (2) *tubulocysts*, including the paroöphoritic or "hilum" cysts, which arise from the tubular relics of the Wolffian body, and the parovarian cysts which arise from Wolffian tubules lying outside the ovary in the mesosalpinx; and (3) *degeneration cysts*, embracing cystic adenoma, a multilocular growth which is by far the most common tumor of the ovary, and some lutein-cysts which arise from degeneration of lutein-cells.

The question of the internal secretion of the ovary is considered in the next chapter.

CHAPTER XII.

INTOXICATIONS, AUTO-INTOXICATIONS, AND NUTRITIONAL DISEASES.

POISONS.

THE action of **bacterial poisons** on the cells has already been considered. It was shown (p. 296) that such substances entered into combination with the receptors of the cells, and that if they were present in large amounts they killed these cells, while if they were administered in gradually increasing quantities, an excess of receptors was produced, and tolerance of the poison in question was thus effected.

Certain organic poisons derived from plants—*abrin* from jequirity, *crotin* from croton oil, and *ricin* from castor oil—act in a similar manner, and antitoxic serums can be produced capable of neutralizing these substances.

Snake-poison.—The poisons contained in snake-venom are not yet identified, but their action resembles that of bacterial poisons. Thus it is said that venom contains a copula capable of activating an alexin already present in the body. An antitoxic serum can be prepared as an antidote, but it seems that the poisons of different snakes differ in their constituents, so that the antitoxin prepared against one variety of snake is ineffectual against the bite of another. Besides a neurotoxin which acts on the nervous system, snake-venom contains substances which affect the coagulability of the blood and break up the corpuscles; and some kinds of venom have the power of dissolving the cells forming the lining of the small bloodvessels, so that petechial hemorrhages are produced.

In the case of the **inorganic poisons,** and of the **alkaloids,** such as strychnine, it would seem that instead of acting on the receptors alone, the poison attacks the main protoplasmic body of the cells. No antitoxic serum can be produced in such cases.

Poisons are generally divided into groups according to their most striking effects upon the body. Thus the **corrosive poisons,** including the strong mineral acids and the alkalies, act principally on the cells with which they come into immediate contact, and cause death mainly by the local lesions produced, and by the pain and shock that ensue. Mineral acids, if given in smaller doses, tend to reduce the alkalinity of the blood, and abstract from the system an increased amount of ammonia to neutralize them. Intense fatty accumulation in the liver may be met with in some instances.

Irritant poisons are closely related to the corrosive poisons, but act rather less destructively upon the tissues with which they come into contact, setting up a local inflammation of varying degrees of severity, and subsequently producing chemical effects upon the whole body or upon particular parts of it. As instances of such substances may be mentioned arsenic, which induces intense gastritis and enteritis by its local action, with remoter effects seen in neuritis, conjunctivitis, and affections of the skin; and cantharides, which acts locally as a vesicant, remotely as a cause of nephritis.

Another large group of poisons (*neurotic*) acts principally upon the central nervous system, producing, on the one hand, drowsiness and coma (alcohol, morphine, etc.), or, on the other hand, convulsions (strychnine) by increasing the reflex activity of the spinal cord.

No sharp line can be drawn between the different groups. Thus alcohol, a narcotic poison, is capable of producing inflammation of the stomach, intestines, and peripheral nerves in the same way as does arsenic, an irritant poison. Phosphorus, which is a local irritant, induces fatty degeneration of the liver as a remote chemical effect. As a general rule, concentrated poisons act locally, while diluted poisons are absorbed into the circulation and act upon distant parts. Different poisons select different tissues for which they have special affinity: thus phosphorus affects principally the liver, cantharides the kidneys, lead or alcohol the nerves, curare the nerve-terminals in the muscles, strychnine the spinal cord, morphine the brain.

When poisons have been taken in small doses over long periods of time, the cells of the body become accustomed to make use of a lymph containing small quantities of the poison, and adapt their chemical processes to this new environment (*drug-habits*). If now the poison be discontinued, the cells cannot immediately become accustomed to do without it, and great physical discomfort, and even death, may ensue if the withdrawal of the poison is sudden (morphine, arsenic).

Excretion of Poisons.—Poisons are eliminated by various different channels—by the urine, by the intestine with the fæces, by the bile, by the sweat, by the saliva, by the gastric glands, and by the lungs. In the process of excretion poisons may cause irritation to the organs by which they are thrown off. Thus turpentine may cause inflammation of the kidney as it passes out by the urine; and toluylene-diamin is said to be eliminated in the bile and to cause catarrhal inflammation of the small bile-ducts, with resulting jaundice. Iodide of potassium is excreted to some extent in the sweat, and gives rise to papular inflammation of the skin by irritation of the sweat-glands. It would seem that the liver plays an important part in neutralizing bacterial toxins which are absorbed from the alimentary canal.

AUTO-INTOXICATIONS.

The term auto-intoxication should, properly, be applied only to poisoning by toxic substances formed in the course of the metabolism

of the tissues themselves. It is, however, often used for conditions of poisoning brought about by the products of bacterial action taking place in the intestine: this is obviously no more an auto-intoxication than any other form of sapræmia. Little is definitely known of the toxins produced. In cases of intestinal obstruction the breath may be offensive, and the urine may contain excess of indican formed from indol-compounds absorbed from the gut. The rise of temperature sometimes associated with constipation in children and in convalescent patients may be due to some poison absorbed from the intestine. Mental depression is sometimes relieved by attention to the bowels; and it has been suggested that some forms of serious mental disease (*melancholia*, *epilepsy*) may be of autotoxic origin (see next chapter). A similar causation has been suggested for some cases of anæmia.

Auto-intoxication properly so-called may arise from (1) retention of secretory materials which should be passed out from the body; (2) from elaboration of some toxic body by perversion of the normal process of metabolism; or (3) by production of excess of some normal product. We may include under this heading, for convenience of arrangement, (4) failure of some organ to produce a substance necessary for the organism.

(1) **Retention of Secretory Materials.**—The kidneys being the most important secretory organs, we naturally look for examples of this form of auto-intoxication to cases of renal disease. Two main conditions at once suggest themselves as instances in which the urinary secretion is abolished: (*a*) obstruction of the ducts of the kidneys (ureters), and (*b*) extensive disease of the kidneys themselves, in both of which conditions anuria or suppression of urine may occur. The phenomena in the two cases are strikingly different. In the former case (*obstructive anuria*) the patient may live for two weeks or more, exhibiting no symptoms beyond increasing weakness and drowsiness, and may at last die suddenly. In the latter case (*non-obstructive anuria*) convulsions rapidly occur, and the patient dies comatose within a few days (*uræmia*). The cause of the difference between the two conditions is not clear: we may suppose that the former state represents the effects of mere retention of waste products which should be excreted in the urine, whereas in the latter the whole of the functions of the kidney are in abeyance, and some "internal secretion" necessary for life is no longer manufactured (see below).

(2) Of **perversion of secretions** owing to disease in the organs which form them, we know nothing as a cause of intoxication: the condition is purely hypothetical.

(3) **Excess of a secretion normally formed in the body** is perhaps responsible for the disease known as exophthalmic goitre or Graves' disease. In this condition there occurs great enlargement of the thyroid gland, along with palpitation and rapid action of the heart, prominence of the eyes, sweating, pigmentation of the skin, tremor of the hands, and great nervous excitability. The patients are generally women. The cause of the onset of the condition is not known. The arguments

in favor of its being due to an excess of thyroid secretion are, first, the almost exact contrast which Graves's disease presents to the malady known as myxœdema (described below), which is proved to be due to defective action of this gland; and, secondly, the fact that somewhat similar symptoms may be produced by administration of large doses of thyroid extract. Good results are said to have been obtained in some cases by treatment with serum or milk derived from animals which have had their thyroid glands removed. It must be admitted that the mode of action of such remedies is not very clear.

(4) **Diminution or Absence of a Normal Secretion.**—Internal secretions—that is to say, substances useful to the organism, poured directly into the blood without the mechanism of a recognizable duct—are supposed to be formed by several organs. The existence of such a function in the case of the thyroid gland is absolutely proved, and in the case of the suprarenal bodies it is fairly well established. The formation of internal secretions by the ovaries, testes, kidney, and pancreas is exceedingly probable; while in the case of the pituitary body and the thymus gland the evidence is less convincing.

Defective **thyroid** secretion is the cause of *myxœdema*. The condition is the same whether the gland be removed by operation or rendered functionless by some inflammatory or degenerative process. In children who are the subjects of congenital defect of the gland (*cretinism*) the symptoms are mental dulness, stunted growth, broad, clumsy hands, coarse features, expressionless face, prominent abdomen, and a tendency to umbilical hernia. In the adult, in whom the disease arises from unknown causes, the face is also expressionless, and has been compared to a mask; the hands are broad and spade-like; the skin is dry, and the hair coarse and scanty; the mind is dull, and thought and speech are slow and hesitating. The pulse is slow, the urinary secretion small, and the bowels constipated. A curious flush is often seen on the malar eminences, while the rest of the face is pale or earthy. These patients are very sensitive to cold. If thyroid secretion be supplied, either by feeding with dried gland-substance, or by injection of an extract of the gland hypodermically, the symptoms of the disease rapidly disappear. The children become bright and intelligent, and growth is resumed; the adults regain their former health and mental capacity.

It is evident that the thyroid gland secretes a substance which is necessary for the nutrition of the cells of other tissues, notably of the nervous system. What this substance is, is not known, beyond the fact that it contains iodine (thyro-iodin). It is scarcely imaginable that more than a very small quantity of it can be daily absorbed, so that it is difficult to suppose that it acts as a direct food-material. It is tempting to suggest that the gland supplies an intermediary body (copula) of some sort capable of facilitating the assimilation of food by the cells; but such a suggestion is merely speculative, and is difficult to harmonize with the phenomena of Graves's disease and its treatment by preparations derived from thyroidectomized animals.

Defective secretion on the part of the **suprarenal bodies** is supposed to be the cause of the condition known as *Addison's disease*. The symptoms of the malady are great weakness; feebleness of the pulse, with very low blood-pressure; pigmentation of the skin and mucous membranes; and sometimes vomiting, diarrhœa, and attacks of syncope. After death the suprarenal bodies are found to be the seats of caseous degeneration due to tuberculosis. These glands normally contain a substance which produces powerful constriction of the bloodvessels; it is natural to attribute the circulatory disturbance met with in Addison's disease to lack of this material. Feeding patients with extract of the glands has not, however, appeared to produce any such beneficial effect as is the case with thyroid feeding in myxœdema; as to the effect of subcutaneous injection of such an extract, the evidence is contradictory. It has been supposed that these glands normally aid in the excretion of pigment derived from breaking down of blood-corpuscles, and that the pigmentation of the skin is due to accumulation of such products.

In the case of the **ovaries**, it is found that removal of these organs induces atrophy of the uterus and an artificial menopause. If they are removed in a pregnant animal, abortion occurs, suggesting that the ovarian secretion is necessary for the nutrition of the fœtus. It has been stated that in cases of carcinoma of the breast, removal of the ovaries is followed by involution of the growth; but this result is not constant. Cases of chorio-epithelioma of the uterus have been found by Lockyer often to be associated with cystic degeneration of the lutein-tissue of the ovaries; and Fraenkel believes that the cells of the corpus luteum are the source of an internal secretion necessary for the life of the fœtus. Removal of corpora lutea causes abortion, but this does not occur if a corpus luteum be grafted in some other part of the body.

The existence of an internal secretion from the **testes** is supported by the effects of removal of these organs in young animals. The special characteristics of the male sex fail to appear. In eunuchs the voice remains shrill, as in women; the beard may not appear, and the general anatomical form of the body approximates to the female type.

Removal of the **pancreas** in animals is followed by a condition identical with the diabetes mellitus of human beings. The urine is increased in quantity, and contains much sugar; there is great thirst and voracious appetite, with rapid wasting of the body; acetone and diacetic acid appear in the urine; and death may be preceded by a comatose condition. In persons who have died of diabetes, there is often found atrophy of the pancreas, extensive fibrosis of the organ, or fatty degeneration; hemorrhage into the pancreas may be associated with diabetes. Opie has found in some cases a hyaline degeneration limited to the special groups of cells called Islands of Langerhans, and other writers also have found these structures diseased. The suggestion has been made that these cells are the source of the internal

secretion of the pancreas. This cannot as yet be regarded as proved; in many cases of diabetes no visible affection of these islands, or indeed of the pancreas at all, is present. It is supposed by some that the internal secretion of the pancreas is necessary for the assimilation of sugar by the cells of the body, especially the muscles; by others that it neutralizes a poison, formed elsewhere, which is capable of interfering with this process.

Disease of the **pituitary body** has been found associated with the peculiar condition known as acromegaly, in which there is great enlargement of the extremities and of some of the cranial bones. The nature of the relation between such lesions of the pituitary body and the disease is not established. It is certain that extensive affections of this body (cancer, gumma) may exist without acromegaly.

The assumption of the formation of an internal secretion by the **kidneys** has been already alluded to as an explanation of the phenomena of uræmia (p. 516). Certain experiments made by Bradford, in which removal of one kidney along with the greater part of the other kidney was followed by increased excretion both of water and of urea, may point in the same direction (p. 500).

The phenomena which result from the removal of some of the above-mentioned organs (pancreas, kidney) may be equally well explained upon the supposition that in health it is the function of these glands to neutralize poisons which otherwise accumulate in the system and cause injurious effects. Possibly such poisonous substances are utilized by the respective glands for their own nutrition; or the latter may form antitoxic materials.

NUTRITIONAL DISEASES.

Under this heading two diseases must be alluded to, namely, gout and diabetes. Little is known of the true pathology of either.

Gout is a condition characterized by the presence of excess of urate of sodium in the blood; this salt is deposited in the cartilages of the joints, and also in bursæ and connective tissues, under certain circumstances which are not fully understood, the precipitation in the joints being accompanied by attacks of severe pain and by symptoms of inflammation. Uric acid, which is converted into sodium urate by the salts in the blood, is supposed to be formed in two ways: (1) By breaking down of the nucleo-albumins of the tissues, and especially perhaps of those contained within the leucocytes; and (2) from similar substances contained in the food. Excess of uric salts in the blood may be produced either by increased formation of these substances, or by diminished excretion of them, or by failure to utilize or destroy them in the metabolism of the tissues. Which process is at fault in gout is not known. The association of the disease with granular kidney might appear to point to defective excretion as the probable cause; but this association is not constant. Gouty attacks are often preceded by disturbances of digestion, and some authors have supposed that the disease

is a toxæmia due to poisons formed in the alimentary tract. Indulgence in alcohol and in rich food is almost certainly a factor in many cases of gout. It is not impossible, on the other hand, that the disease is due to a defect of assimilation, dependent upon a perversion of the normal chemical action of the cells. The most surely established fact in its etiology is its hereditary transmission. Males are more often affected than females—a peculiar feature of most hereditary maladies.

Diabetes is a disease characterized by the continued passage of large quantities of urine containing sugar (dextrose). Along with this there are wasting, increased appetite, and great thirst. The appearance of sugar in the urine is due to the presence of this substance in the blood in largely increased amount. As with the urates in gout, so with the sugar in diabetes, excess may be due either to increased production or to diminished excretion, or to defective utilization of the substance in the chemical life of the cells. To decide definitely which of these causes is at work is not at present possible. Claude Bernard, soon after his original discovery of the existence of glycogen in the liver, showed further that puncture of the floor of the fourth ventricle would produce glycosuria; this was apparently due to disturbance of the circulation in the liver, with resulting rapid conversion of glycogen into sugar and passage of this sugar into the blood. The glycosuria which accompanies some forms of cerebral injury and disease is almost certainly of this nature; it is more persistent than the transitory glycosuria of the "puncture" experiment merely because the cause persists. Such cases are perhaps hardly to be called diabetes. True diabetes may, however, result from traumatism of various kinds, and in such instances some other factor seems to enter into the causation of the condition. A condition almost exactly identical with diabetes mellitus is produced by poisoning with the glucoside phloridzin. Injection of suprarenal extract produces a very similar condition, apparently by a direct reducing action upon the pancreas. The effect of experimental removal of this organ has been already mentioned (p. 518).

In true diabetes it has been suggested (1) that the liver is unable to retain the glycogen which is usually stored up in it, and which therefore passes rapidly into the blood (Cl. Bernard); (2) that some ferment normally contained in the blood, by which sugar is destroyed, is absent in diabetes (Lépine); (3) that some toxin is formed which interferes in some way with the production or utilization of sugar; (4) that carbohydrate food, which is usually absorbed from the intestine in the form of fat, is in diabetes absorbed as sugar, which passes into the blood-stream and acts as a poison (Pavy). There are not at present sufficient data available to settle which, if any, of these views represents the true nature of the disease. In severe cases of diabetes sugar is undoubtedly formed by breaking down of the tissues of the body: it is impossible to be sure that this process is not active throughout the affection.

In diabetes it is found that the alkalinity of the blood is diminished, owing to the formation in the system of organic acids (aceto-acetic, β-oxybutyric, etc.). This **acid-intoxication** is very characteristic of diabetes, in which it occurs with the greatest intensity; it is found, however, in other conditions, such as infantile enteritis and starvation. The source of the acids formed is not certainly known, but there is reason to believe that they arise by the breaking down of fat, to which oxybutyric acid is closely related. Under normal circumstances oxybutyric acid is excreted as acetone, the substance which gives the sweet smell to the breath of diabetic patients; but in diabetes this acid and aceto-acetic acid may appear in the urine along with the acetone, which is present in very large amount. Probably as much acetone may be eliminated from the body by the breath as in the urine. The organic acids enter into combination with ammonia derived from the proteids of the body, and are excreted as ammonium-salts in the urine. The effect produced is equivalent to poisoning by a mineral acid (p. 514); indeed, Bunge held that the acid substance which actually accumulates in the body in acid-intoxication is sulphuric acid.

It is now held that the *coma* in which patients suffering from diabetes often die is due to the acid-poisoning. Attempts have been made to identify the toxic agent with one or other of the substances formed—acetone, β-oxybutyric acid, β-amido-butyric acid—but without success.

The nature of **obesity**, which appears also to constitute a "nutritional disease" in many instances, has already been discussed (p. 48).

CHAPTER XIII.

PATHOLOGY OF THE NERVOUS SYSTEM.

INTRODUCTION.

THE morbid processes affecting the nervous system are numerous and varied, but they are usually divided into two groups: (1) *Organic disease*, (2) *Functional disturbance*. Such a classification depends upon whether or not symptoms observed during life can be associated with changes of the nervous system, gross or microscopical, recognizable after death. As was previously stated (p. 21), functional disorder necessarily involves the existence of structural change, although this may be so minute (molecular) as to escape notice. Many diseases of the nervous system which are classed as functional are probably due to the action of poisons; others depend upon inherited instability (tendency to chemical change) of the cell-substance. The paroxysmal neuroses and psychoses—*e. g.*, epilepsy, migraine, certain forms of mania and melancholia—are not improbably brought about by causes belonging to one or other of these last categories.

Morphology.—The histological elements which make up the nervous system are derived from the outer and middle layers of the blastoderm. The epiblast furnishes the nerve-cells and their processes, the neuroglia, and the epithelium lining the ventricles and the central canal of the spinal cord. The mesoblast furnishes the bloodvessels, lymphatics, and membranes of the brain, and the neurilemma or nucleated sheath of Schwann. The origin of the myelin-sheath is not known. The study of the development of the nervous system, and observations made by the methods of Golgi or by modifications of them, have demonstrated that in all vertebrates the true nervous elements consist of independent complex cells which are generally spoken of as "neurons." The morphological characters of all *neurons* at one period of development are fundamentally similar—viz., a cell consisting of spongioplasm and hyaloplasm containing a nucleus and nucleolus. From this cell processes grow out, and these processes, which are probably made up of delicate fibrillæ, are continuous with, and of the same biochemical nature as, the framework of the cell-substance. One process of the cell gives off collaterals and becomes the *axon* of a nerve-fibre; the others, termed *dendrons*, branch many times like a tree, and terminate in an apparently inextricable network (Fig. 304). Within the cell-body, lying in the spaces of the spongy network (*spongioplasm*) is the so-called *hyaloplasm*. The staining-method of Nissl shows that the

spongioplasm and hyaloplasm differ in chemical constitution, for the former is unstained by basic aniline dyes, and is therefore termed "achromatic," whereas the latter is "chromatic" and readily takes the stain. The blocks of colorable substance, seen in the large motor cells of the brain and spinal cord, are termed *Nissl bodies*. They consist of extremely fine particles suspended in a fluid, and are said to represent a store of energy or food. It will be observed that Nissl bodies in the

FIG. 304.

A B

A. Diagrammatic representation of the dendron and dendrites of a cortical pyramidal cell, with the tangential fibres running at right angles.

B. Exact copy of a microphotograph of the dendron and dendrites with tangential fibres. From a section of the brain of a dog kept four hours under chloroform. Stained by Cox's method. All the processes are seen studded with little buds or gemmules. Contrast this with A.

form of spindles exist also on the dendrons; in fact, the axon can always be recognized by the absence of these chromatic bodies. In all probability these Nissl bodies do not exist in the living cell, but precipitation occurs on the death of the nerve-cell, as in the case of myosin from dead muscle-plasma, since the Erhlich *intra vitam* methylene-blue method does not exhibit Nissl bodies. The value of the results obtained by the Nissl method is, however, undoubted. For the study of pathological alterations it matters little whether the Nissl bodies are preformed bodies existing *intra vitam* or are the result of precipitation, as long as it is known that a healthy nerve-cell differs from

a diseased nerve-cell by the appearance of the stained substances (*vide* Plate).

The method of Golgi, or modifications of it, teaches us nothing of the internal constitution of the neuron, and is not likely to yield such valuable results from a pathological as it has from an anatomical point of view. The fundamental conception of the neurons as independent morphological units, in contiguity but not in continuity one with another, yet withal possessing physiological association and mutual interdependence, is of the greatest importance in the study of nervous diseases, and especially as affording an explanation of those morbid conditions which are termed functional. The chrome-silver and mercury methods have shown that studded all over the branches of the dendrons (*dendrites*) are little buds or gemmules (Figs. 304 and 305); and that fine branches (*collaterals*) are given off from the axon. These facts have also been demonstrated in vertebrates by the *intra vitam* methylene-blue method. A neuron in a series or system, although in intimate physiological relation with the dendrites of the next in the series (*e. g.*, the motor efferent system, Fig. 333) is not in anatomical connection with them.

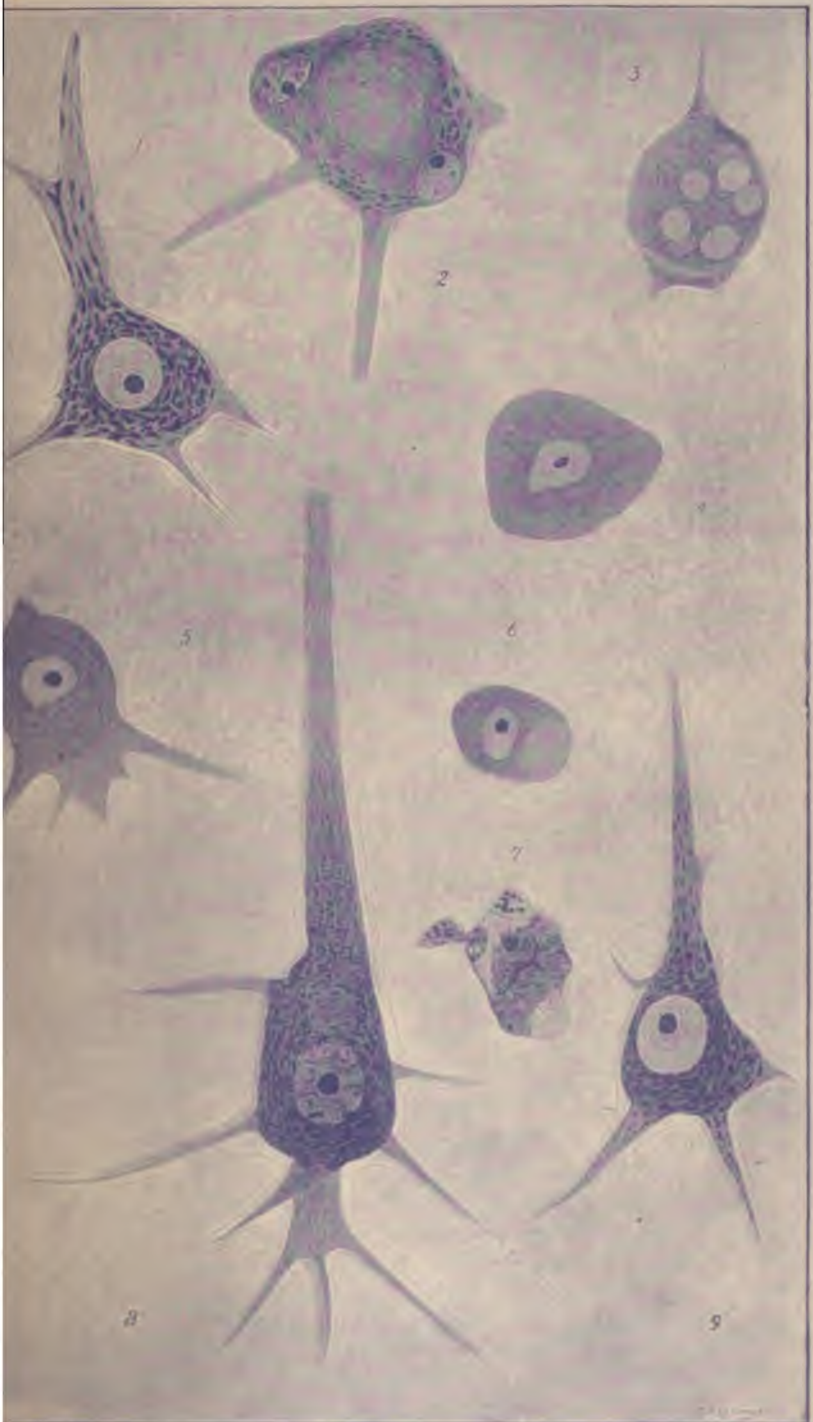
The cerebrospinal neurons may be divided into *afferent*, *efferent*, and *association* systems, but the last are by far the most numerous, and constitute the great bulk of the brain.

Theories of Interneuronic Relationship.—All the above systems are in physiological relationship. The nervous impulses or molecular vibrations are transmitted toward the nerve-cell by the dendrons and away from it by the axon. In a system or series of nervous units with multitudinous points of contact, it is conceivable that physiological interneuronic relations may vary owing to retraction of the dendritic processes of one from contact with the terminal arborizations of the axons of another, so that the molecular vibrations may pass through systems, or communities, of neurons with a variable degree of intensity or rapidity.

Many apparently inexplicable problems relating to normal and pathological functional conditions of repose and activity could be explained

Description of Plate.

Plate.—1. Large Betts cell, fairly normal, showing the Nissl granules in the body of the cell and on the processes. 2. Degenerated cell from anterior horn in a case of general paralysis. 3. Ditto, more advanced degeneration, with vacuolation. 4. Posterior spinal ganglion-cell, showing the different distribution of the chromophile substance. 5. Degenerated cell from experimental cerebral softening. Compare this with 1 and 9. The cell is swollen, the Nissl granules are absent and replaced by a fine dust of colorable substance staining the cell uniformly. 6. Posterior spinal ganglion-cell, showing pigmentation at one pole. 7. A pyramidal cell from the cortex, acute softening from ligature of cerebral arteries, showing phagocytes sticking to the dead cell and devouring it. 8. Large pyramidal cell of the cortex cerebri, showing absence of the Nissl granules in the body and the processes; uniform staining. From a case of hyperpyrexia. 9. Large pyramidal cell of the cortex cerebri, showing little, if any, change. From a case of septicæmia of considerable duration, but without high fever. All the figures are exact representations of microphotographs. Magnification of 1, 2, 5, 8, 9 is 700 diameters; of 3, 4, 7, 350 diameters; of 6, 200 diameters.



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by such a theory of association and dissociation of the interneuronic connections. The theory, however, as yet rests upon a very slender foundation of facts. Movements in the nerve-cells of a minute aquatic animal having been observed under the microscope, it was conceived that the terminal twigs of the nerve-fibre processes might elongate and so come into better contact with the dendritic processes of the next neuron of the series. This led to the idea that sleep and unconsciousness from anæsthetics, and narcotics, also trance and hypnotic state, hysterical paralyses and anæsthesiæ and other conditions such as cata-

FIG. 305.

A. Pyramidal cell of cortex. From case of acute softening, due to experimental ligature of vessels. Stained by chrome-silver method. Shows practically normal appearances of the cell and its processes, but by Nissl method profound changes were evident. It is, therefore, probable that this method is not suitable for studying acute changes in the neurons.
B. Normal neuroglia-cell. Stained by chrome-silver method.

tonia, catalepsy, etc., might be due to retraction of the terminal twigs of the sensory neurons on the surface of the brain, so that contact is broken and the transmission of nervous currents is thereby interrupted. The attempt has been made to find a basis for this theory of retraction of the terminal buds or points of contact of the branching processes of the dendrons by fixing in various fluids small pieces of the brain of animals which had been anæsthetized with chloroform, morphine, or other narcotics, and comparing the appearances presented by the dendrons with those seen in the brain of an animal killed suddenly. The results obtained have been divergent. *A priori*, it would seem more

probable that cerebral activity is associated with a cutting off of the great majority of interneuronic connections and the strengthening of the current traversing a few; that during repose or under narcotics there is a general expansion of the gemmules, due to exhaustion of their contractility; and that thus, all the neurons being in contact, nervous currents are so diffused that they are not of sufficient intensity to rise into consciousness.

The other histological elements derived from the epiblast are the neuroglia-cells and fibres. Their function is to support the neurons. According to Weigert, the cells are independent of the fibres, but it is generally believed that the neuroglia-cells have numbers of branching processes (Fig. 305) which pass in all directions between the processes of the neurons, and various theories have been elaborated giving to the neuroglia-cells important functions apart from mere supporting properties. Some neuroglia-cells have an expansion on the minute bloodvessels, and the opinion has been expressed that they are capable of contracting, and thereby causing expansion of the vessel, thus determining more blood to nervous structures which are in functional activity. They have also been thought to have the function of contracting and drawing together thereby the terminal processes of the neurons.

Causes of Disease.—A correct understanding of neuropathology involves the study of: (1) The causes which give rise to nervous diseases; these are often complex. (2) The changes in the structure and functions of the nervous system brought about by these causes.

The causes of pathological processes occurring in the nervous system may be divided into *internal* and *external*, but it may be remarked that in nearly all cases except those due to direct injury the two are more or less combined.

INTERNAL CAUSES.—Of all the causes of nervous disease, *hereditary predisposition* stands pre eminently first. It may come directly from one or both of the parents, or from more distant ancestors. Strictly speaking, it is the tendency to nervous disease and insanity rather than the disease itself that is inherited, and this is frequently spoken of as "neuropathic tendency." There are, besides, a number of *inherited diseases* which affect members of a family; the disease frequently commencing in each individual at about the same age. These are termed "family diseases" —*e. g.*, *hereditary ataxia* (Friedreich's disease), *hereditary chorea*, and various forms of *idiopathic muscular atrophy*. Alcoholism and syphilis in the parents, especially if one or both come from a neuropathic stock, frequently engender, by the production of defects in the germinal plasm, arrest, imperfect development, or premature decay of the neurons, causing *idiocy*, *imbecility*, and *dementia*. Like all cells, the neuron depends for its development, life, and functional activity upon a suitable environment. It must also possess an inherent vital energy, by which it can assimilate and store up nutrient material, which may be regarded as *potential* energy, to be converted into nerve-force as

required. A constant constructive and destructive bio-chemical process occurs in the nervous elements, and in a healthy nervous system the *balance of potential* is high, and the sense of fatigue is the natural indication for sleep and repose by which nervous energy may be recuperated. It may be conceived that in some portions of the nervous system, especially the brain, there may exist systems, or groups of neurons, with *inherited low potential*, rapidly becoming exhausted, and especially liable, therefore, to *depression of function*—*e. g.*, hysterical paralyses, anæsthesiæ, and melancholia; or the bio-chemical substance, which represents potential, may possess an *inherent chemical instability*, and readily fulminate when an appropriate stimulus occurs, thus acting as a centre of discharge of nervous energy and causing *excessive functional activity*, which may be manifested by mental or bodily symptoms, *e. g.*, mania and epilepsy. Lastly, there may be functional disturbance of the harmonious interrelations of the nervous elements, with *failure of co-ordination*—*e. g.*, chorea.

EXTERNAL CAUSES, producing morbid changes in the nervous elements, are dependent upon (A) abnormal conditions of the blood and lymph, by which the neurons are poisoned, and their metabolism affected; (B) excess or deficiency of normal excitation, or the existence of abnormal excitation.

A. **Abnormal Conditions of Blood and Lymph.**—The immediate environment of all the cellular elements of the body is lymph. In the central nervous system a special form of lymph, the cerebrospinal fluid is secreted by the choroid plexuses. The lymph serves as the medium of exchange between the blood and the tissues, and the essential causes of change in the environment of a nerve-cell are alterations in the quantity and quality of the blood-supply.

1. **The Quantity of Blood-supply.**—A frequent cause of disease of the nervous system is a failure of the blood-supply to some portion of the brain. (See Embolism and Thrombosis, Chapter VII.)

2. **Quality of Blood-supply.**—Insufficiency of oxygen due to anæmia leads to functional depression, lassitude, and mental fatigue. Impoverishment of the blood in women, by frequent pregnancies and excessive lactation, causes neuralgia, nervous exhaustion, and, in the *neuropathic* subjects, hysteria, neurasthenia, melancholia, and mania. Probably there is an alteration in the composition of the blood, in the nature of an auto-intoxication or a "sub-minimal" deficiency. The most striking examples we have, however, of the effect of absence or "sub-minimal" deficiency of a normal constituent of the blood upon the development and functions of the nervous system are afforded by *cretinous idiots*, whose brains are arrested in development in consequence of the absence of the thyroid gland, and by the subjects of *myxœdema*. The proof of this is shown by the disappearance of the nervous phenomena of myxœdema on making up the deficiency by administration of the gland by the mouth.

More important than defects of necessary material are the *toxic* causes of diseases of the nervous system. They may consist in:—

(a) *Excess of Normal Constituents in the Blood.*—Carbonic acid, and

nitrogenous waste-products, may be given as examples of normal constituents which, if in excess, give rise to symptoms of disease. Again, in *Graves's disease*, nervous phenomena in the form of exophthalmos, palpitation, fine tremors, and mental excitement may be ascribed to excess of thyroid secretion escaping into the blood.

(*b*) *The presence in the blood of abnormal constituents* is the most important extrinsic cause of nervous disease, and we may consider the subject under the following headings: (1) *poisons produced within the body, by perverted function of the organs or tissues* (*auto-intoxication*), or *by the action of micro-organisms upon the living fluids and tissues of the body;* (2) *poisons introduced into the body from without.*

(1) *Poisons Produced within the Body.*—The best examples of auto-intoxication are afforded by *uræmia*, the nervous manifestations of which are headache, drowsiness or coma, and epileptiform convulsions; sometimes symptoms of polyneuritis; excess of *uric acid* in the blood which is associated with high arterial pressure, headache, and nervous irritability; *diabetes* (a result of imperfect metabolism) may cause multiple neuritis and coma, the latter being often heralded by *acetonæmia*, which may be regarded as a form of auto-intoxication; *cholæmia*, resulting from obstructive jaundice, may be attended by stupor and psychical depression. Again, the rapidly fatal results attending *acute yellow atrophy of the liver*, the profound changes in the urine and blood, the jaundice accompanied by the nervous phenomena of delirium, motor irritation, delusions, stupor and coma, demonstrate the important part the liver plays in maintaining the normal quality of the blood. In *pernicious anæmia*, and in other grave anæmias, degenerative changes in the spinal cord, of the nature of a combined sclerosis, are frequently found, and are probably not so much due to the deficiency of red corpuscles as to some toxic substance arising from imperfect metabolism. Choline, a product of the breaking-down of nervous tissue, has been shown by Donath to be capable of producing convulsions.

We do not know the nature of the *rheumatic* poison, but we know that it is especially liable to be followed by, or associated with, chorea and hyperpyrexia, indicating a selective action of the poison upon the cells of the cortex cerebri.

Examples of poisons due to micro-organisms occur in many infective diseases—*e.g.*, typhoid fever, typhus, smallpox, scarlet fever, measles, influenza, pneumonia, septicæmia, tuberculosis. Delirium is a frequent complication in these diseases; it may be the result of the high fever, or of the poison, or of the fever and the poison combined. In severe cases stupor and coma may occur, and it has been shown that in this extreme stage the nerve-cells of the cerebral cortex, and also of the spinal cord, undergo an acute morbid bio-chemical change (*vide* Plate). These particular poisons have not a selective action upon any special part of the nervous system, but many cases of neurasthenia, insanity, neurosis, and neuritis date their onset from an acute specific fever.

In cerebrospinal meningitis, posterior basic meningitis, tubercular meningitis, acute delirious mania, and leprous neuritis the inflamma-

tion of the enclosing and supporting tissues is due to the growth therein of the specific organism, and, by analogy, we might suppose that syphilitic affections of the nervous system are due to some specific micro-organism attacking its enclosing, supporting, and vascular tissues.

Some poisons have a selective influence upon some part of the nervous system. The syphilitic poison is the most important factor in the production of two progressive degenerations of the nervous system, one affecting especially the afferent conducting tracts of the spinal cord, viz., locomotor ataxy; the other affecting especially the frontal and central convolutions of the cerebral hemispheres, viz., general paralysis of the insane. A striking instance of the *selective action* of the *syphilitic* poison is shown in the fact that only in persons affected with acquired or inherited syphilis is the symptom known as the *Argyll-Robertson pupil* found (this is the absence of reflex contraction of the pupil to light, while that to accommodation persists); seeing that this is the most common objective phenomenon in the two diseases mentioned, it strengthens the presumption, based on experience, that the syphilitic poison is the cause of these diseases in the majority of instances. These diseases are often termed "parasyphilitic" (Fournier) and are degenerative processes, the result of an impaired vitality of the neurons, causing premature decay and atrophy. Again, syphilis when it attacks the supporting, enclosing, and nutrient vascular mesoblastic tissues shows a predilection to affect structures about the base of the brain; thus paralysis of the third nerve is almost pathognomonic of this disease. In *rabies*, although the whole nervous system is charged with the poison, the medulla oblongata (as shown by the symptoms) is especially affected. Again in *tetanus* the bacilli elaborate a virulent poison which affects particular groups of neurons. The fact that "lockjaw" nearly always occurs first shows that the poison selects the *motor nucleus of the fifth nerve.* Experiment has proved that the tetanus-toxin, if mixed with an emulsion of nervous matter before injection into an animal, loses its toxicity, thus showing its affinity for nervous matter. The receptors (side-chains, of the nerve-cells) fix the toxin to themselves, just as do molecules of free antitoxin, so that none remains available to poison the animal. Another example is offered by *diphtheria;* a neurotoxin is produced by the local action of the bacilli, the effects of which are shown by paralysis of the soft palate, paralysis of the muscles of accommodation, weakness and inco-ordination of the limbs, which may amount to paralysis, absence of knee-jerks, and often skin-anæsthesia, and the disease occasionally terminates fatally from cardiac or respiratory paralysis.

(2) *Poisons Introduced into the Body.*—The most widespread and potent cause of vervous and mental disease is the abuse of *alcoholic stimulants.* To people with unstable nervous systems a small quantity of alcohol acts as a poison. It may produce acute delirium with fine tremor, and generally visual hallucinations of a horrible nature, indicating acute toxic influence on the brain. This acute form of alcoholic poisoning is much commoner in men than in women, and it is remarkable how a severe illness, such as pneumonia, will bring out delirium

tremens in a drunkard. Alcohol acts especially upon the higher centres of the brain, and a drunken man may exhibit "the abstract and brief chronicle of insanity, going through its successive phases in a short period of time" (Maudsley). The functions of the brain are stripped off successively in an inverse order to their development, viz., moral control and responsibility, judgment and deliberation, attention and concentration, memory and receptivity. The effect on the nervous system of chronic tippling is dementia, a very characteristic manifestation of the mental degradation being absence of knowledge of time and place, personal illusions, and *loss of memory of recent events*, indicating a failure of receptivity and of the formation of memory-pictures in the higher centres. The improvement which generally occurs when total abstinence is enforced shows that the poison has damaged, but not destroyed, the nervous elements. Besides mental symptoms of alcohol-poisoning there are frequently sensory disturbances and motor paralysis due to polyneuritis affecting especially the lower limbs, although the upper limbs and even the respiratory muscles may be affected in severe cases.

Lead is peculiar in selecting the nerve which supplies the extensor muscles of the wrist and fingers, so that *dropped wrist* is almost characteristic of this form of toxic neuritis. Lead also produces a chronic inflammation of the cerebral cortex (*encephalitis saturnina*), which gives rise to a complex of symptoms, viz., dementia, loss of memory, weakened intellect, paresis and epileptiform seizures, hallucinations of sight and hearing, and mental exaltation or depression. *Arsenic* has a special selective influence upon the peripheral nerves, causing polyneuritis. Generally all four limbs are affected. Sometimes psychical troubles and in rare cases epilepsy occur. Workmen at India-rubber factories, owing to the inhalation of the fumes of *bisulphide of carbon*, may suffer with severe mental symptoms and polyneuritis. There are a certain number of poisons besides alcohol which act on the nervous system when continually entering the body as the result of a *habit*, viz., absinthe, ether, cocaine, opium, morphine, haschish, and tobacco. Not only does absinthe produce epileptic fits when taken for some time, but if intravenously injected into an animal produces epilepsy.

Beri-beri, or *kakke*, a polyneuritis endemic in the East, is by some authorities believed to be due to a micro-organism, and *African lethargy*, or *sleeping sickness*, a chronic meningo-encephalo-myelitis, is probably due to some toxin produced by the trypanosome associated with this disease (p. 262).

Pellagra is an affection of the skin associated with degenerative changes in the brain and spinal cord. The people so affected exhibit a fatuous melancholy and suicidal impulses, sometimes mania. It is supposed that this disease is due to the consumption of bad maize, containing some poisonous substance.

Ergotism is a disease due to consumption of bread made of rye which has been attacked by the ergot fungus. The poison thus introduced produces progressive degenerative changes in the brain and spinal cord.

In *botulism*, due to eating decayed meat and fish infected with the Bacillus botulinus, paralysis of the ocular muscles is an important feature.

B. **Deficiency or Excess of Normal Stimulation or Existence of Abnormal Stimulation.**—Structure and function are mutually reciprocal and interdependent. A structure which is not used will gradually lose its function, while its nutrition will also suffer, and in time atrophy may occur. Amputation of a limb in early life causes atrophy of the nervous structures which presided over the sensation and movement of the part. This is seen in both the gray and the white matter of the spinal cord of the same side. A function not used will gradually disappear, and become more and more difficult to evoke. This fact is of importance in functional neuroses and psychoses—*e. g.*, hysterical paralysis and melancholia—because the longer mental or bodily function is left in abeyance the more likely is the defect to become permanent. The converse is also true—the longer a perverted function exists, the more unlikely is it to disappear. Thus auditory hallucinations, a very important and frequent symptom in the insane, commence with indistinct noises; these are followed by *voices;* and eventually the voices are so distinct and real that the greater part of the patient's psychical existence is concentrated upon, and determined by, this abnormal stimulus from within. Thus are shown the progressive strengthening and *fixation of the perverted* functions of the mind, and progressive weakening and *dissolution of the normal functions.*

Abnormal stimulation from without. (1) *Psychical Stimuli.*—Mental pain in the form of grief, worry, anxiety, fright, and shock, violent emotions (pleasurable or painful), disappointed love, sexual excesses or perversions, and excessive brain-work frequently precede and determine, in persons with the insane or neuropathic taint, various forms (*a*) of psychoses, *e. g.*, mania, melancholia, delusional insanity, (*b*) of neuroses, *e. g.*, chorea, hysteria, epilepsy, hystero-epilepsy, (*c*) of organic brain disease, *e. g.*, apoplexy, thrombosis, and general paralysis. The effect of stress in determining neuritis and degenerative processes in the central nervous system can often be observed in practice. The most striking examples of *psychomotor functional paralyses* from stress are afforded by writers', piano players', violinists', and typewriters' cramp, and hammerman's palsy.

(2) *Physical Stimuli.*—Visceral reflex irritation may act as an exciting cause of neuroses and psychoses: thus, intestinal worms, teething, and *indigestible food*, severally or combined, often produce in infants and rickety children convulsions, spasm of the glottis, and tetany. Various functional and organic diseases of the female reproductive organs act as exciting causes in the production of hysteria, hystero-epilepsy, melancholia, and mania; moreover, paroxysmal attacks in these diseases are more liable to occur at the menstrual period or the menopause. The irritation of a carious tooth may produce trigeminal neuralgia. Wax in the ear may occasion vertigo and tinnitus aurium, and errors of refraction may be the cause of attacks of migraine, and even tend to excite

epileptic fits in a person suffering from epilepsy. Numerous other examples of peripheral disturbance could be mentioned as exciting causes of nervous affections, *e. g.*, irritation of the terminals of the vagus in almost any part of its widespread visceral distribution may lead to reflex vomiting. The characteristic pain of angina pectoris which radiates down the inner side of the left arm, is explained by the fact that the cardiac branches of the sympathetic arise from the same segments of the spinal cord as the sensory branches of the ulnar nerve; consequently the pain is referred to the corresponding skin-area supplied by this nerve. This is one example of a great number of *referred pains*.

DEGENERATION AND REGENERATION.

There is no evidence to show that neurons once destroyed in an adult animal can ever be replaced; whatever return of function may occur is due to the fact that other associated neurons carry on the function. Waller showed that when a nerve is cut off from its trophic and genetic centre (cell of origin) degeneration of the whole of the portion so separated takes place. This process of degeneration neither creeps up nor down, but the morphological changes are simultaneous throughout the whole peripheral portion of the cut nerve. Whereas there is conclusive proof that regeneration of peripheral nerves takes place, there is no evidence to show that fibres in the central nervous system, when they are separated from their trophic and genetic centres, undergo regeneration. When a peripheral nerve is cut across, or even an inch or two is cut out, regeneration will in time take place. The process of regeneration will be greatly hastened if the divided ends of the nerve are sutured; or if a piece has been excised regeneration can be hastened by introducing a piece of nerve, or a piece of catgut or a decalcified chicken bone between the cut ends to conduct the outgrowing axons from the proximal portion of the nerve. The rapid return of sensibility which sometimes takes place after a nerve has been cut and sutured has led some authorities to believe in union by first intention. This, however, is not so. It is due to the overlapping of sensory nerves in the skin and the opening up of new and previously unused paths when the main road is blocked.

Histology of Degeneration.—When a nerve is cut across *Wallerian degeneration* occurs. This process affects the peripheral portion of the cut nerve. It was previously taught that no changes occurred in the central portion of the neuron, but the researches of Nissl, Marinesco, and others prove that bio-chemical changes occur in the trophic and genetic cells of origin. We have, therefore, to consider the changes in the peripheral portion of the cut nerve, the changes in the nerve-cell, and the process of regeneration.

After cutting a nerve the following changes can be observed in preparations of the peripheral portion stained with osmic acid. Within twenty-four hours the myelin commences to lose its straight, regular outline and to exhibit an irregular appearance. The next day changes

can be recognized in the axis-cylinder process; it is swollen in some places, thin in others, while the myelin commences to fragment, and a little later the axis-cylinder ruptures. On the third day the nuclei of the primitive sheath show signs of mitosis, the prelude to nuclear and cellular proliferation. On the fourth or fifth day there are evidences of proliferation of the nuclei and surrounding protoplasm, and these nuclei with surrounding protoplasm breaking through the sheath of Schwann cause a further fragmentation of the myelin, which continues until the tenth day (Fig. 306). The appearance of the degenerated fibres on the eighth to the tenth day is characterized by swellings alternating with constrictions. The swellings are due to accumulations in corresponding parts of the nerve-tubules of degenerated myelin-globules, proliferated nuclei and protoplasm. On the fifteenth day the fibres in the greater part of their course consist merely of tubes containing protoplasm and proliferated nuclei, and little or no myelin; but here and there alternating with the constricted portions are fusiform swellings caused by distention of the sheath of Schwann with drops of liquefied myelin, nuclei, and often curled-up portions of the axis-cylinder. The degenerated myelin is absorbed by leucocytes and fatty granule-cells are thus formed. The nerve consists eventually of fibrous connective tissue and shrunken tubes containing proliferated nuclei and protoplasm. The latter becomes fibrillated and thus prepares the way for the new axis-cylinder processes which will grow down from the central stump. This process commences about the fourth or fifth week by a sprouting of the axis-cylinder process; this divides into several separate fibres, which insert themselves into and between the old primitive sheaths. Growth of the axis-cylinder always begins from a node next above or close to the section. The number of new axis-cylinder processes is in excess of the nerve-fibres destroyed, consequently it may be presumed that many atrophy and disappear (Fig. 307). At first the new fibres are non-medullated, but later they acquire a medullated sheath and nodes of Ranvier, which are at first placed at short intervals, as in young nerves. In the scar, primitive sheaths are at

FIG. 306.

Fibres from the peripheral end of a nerve ten days after section. Stained with osmic acid. One fibre shows the masses of degenerated myelin, the other is healthy. × 200

first wanting, but they ultimately form from the surrounding connective tissue. It may take months or a year or more before function is restored. The time varies with the length of nerve beyond the point of division, and with the distance between the cut ends. Sensation returns before movement. It is not generally admitted that regeneration can occur from the periphery, although there is some evidence forthcoming to that effect. It has long been known that the myelin and axis-cylinder

Fig. 307.

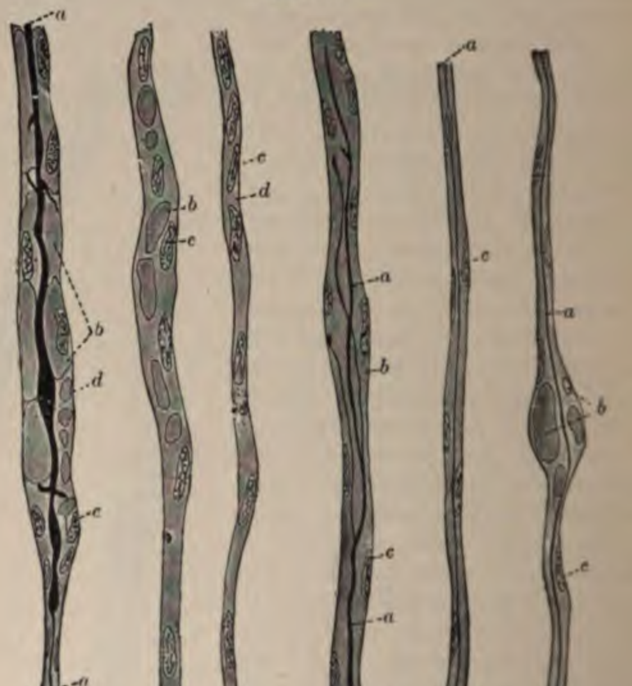


Diagram modified from Howell and Huber, showing stages in regeneration of a peripheral nerve. 1, central end of nerve 21 days after section; 2, peripheral end of nerve 21 days after section; 3, central end of nerve 100 days after section, showing sprouting axis-cylinder with three branches; 4 and 5, peripheral end of nerve 100 days after section. *a*, axis-cylinder; *b*, myelin; *c*, nuclei.

undergo degenerative changes in the central portion of the cut nerve, as far as the node of Ranvier above. It has now, however, further been shown, that if a nerve, *e. g.*, the hypoglossal, be cut on one side and sections of the medulla be stained by Nissl's method, microscopical examination of the cells of origin forming the nucleus of that side presents a marked contrast in shape and mode of staining as compared with the other, indicating a *reaction of injury* in the trophic and genetic centre. A short time after the section of the nerve the cell-bodies and

nuclei of the group of neurons concerned appear somewhat swollen, and there are marked changes in the appearance of the protoplasm. The chromophilic elements are no longer distinct, but are replaced by a dust of fine colored granules, and there is a diffuse staining of the achromatic substance. About the time when the axis-cylinder begins to grow out the normal chromophilic character of the cell begins to return, and eventually, when function has been restored, the majority of the cells present a normal appearance.

Diseases of Nerves.—It is convenient here to consider the subject of *neuritis;* for it must be remembered that *parenchymatous neuritis* really is a degenerative change of spinal, motor, and sensory neurons, although the effects of the toxic agents in the blood are only visible in the remoter portions of the neurons. "Stocking anæsthesia" of the legs and "glove anæsthesia" of the arms, characteristic of polyneuritis, indicate that the sensory disturbance does not correspond to spinal segmentation, but is dependent upon distance from the trophic and genetic centres, and possibly, also, upon distance from the heart, and consequently impaired circulation. In four fatal cases of alcoholic polyneuritis examined by Mott, marked changes were present in the cells of the anterior horns and the posterior spinal ganglia.

Parenchymatous neuritis is toxic in origin and usually symmetrical, and affects a number of nerves (*polyneuritis*); it may be associated with some interstitial change, but generally this is secondary to the degenerative process.

The changes in the nerves are those of primary Wallerian degeneration, viz., breaking up of the myelin, proliferation of the nuclei of the sheath of Schwann, swelling of the axis-cylinder in some places, attenuation in others, and finally its rupture and destruction. The process commences at the periphery, and spreads centreward. If the poison is eliminated before destructive changes have occurred in the cells of origin, it is possible for regeneration to occur, but often the paralysis is permanent. The difference in the microscopical appearances between parenchymatous neuritis and degeneration from section of a nerve is that in the former the fibres are much more unequally affected, some exhibiting comparatively little change, while others show advanced degeneration (Fig. 308).

Interstitial neuritis is an inflammation affecting the vascular, interstitial and supporting connective tissue, sometimes causing permanent, sometimes temporary loss of function according to whether the inflammation is productive of degenerative changes in the nerve-fibres or not. It may occur as a result of injury or cold, especially in a rheumatic or gouty subject, sciatica and Bell's paralysis affording examples of this affection. In anæsthetic leprosy and syphilis the interstitial vascular connective tissue is the seat of a specific inflammatory process; the former disease is known to be due to a specific bacillus, and the latter is almost certainly due to a micro-organism.

Degeneration of the Central Nervous System.—The methods employed for studying Wallerian degeneration of the central nervous

system, taking, for example, the spinal cord, where the afferent and efferent tracts are clearly defined, are as follows: If posterior spinal roots be cut, or there be a transverse lesion of the spinal cord, it is possible if the patient survive for ten days to recognize naked-eye changes in definite tracts of the spinal cord, provided the spinal cord be suspended

Fig. 308.

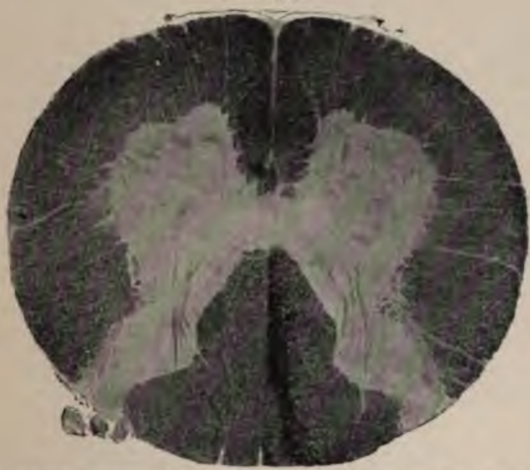
Section of anterior tibial nerve. Showing parenchymatous degeneration in a case of beriberi of eight weeks' standing.

in Müller's fluid for a month or so (Fig. 309). The cord thus hardened is cut transversely and the degenerated tracts are recognized by their *lighter yellow color*, as compared with the healthy white matter which is now stained a brownish yellow. For microscopical examination of such an early degeneration, there is no method to compare with that of Marchi. It consists in placing thin transverse slices of the central nervous system thus hardened in a solution of *one* part of a 1 per cent. solution of osmic acid and *two* parts of Müller's fluid for one to three weeks, then washing for several days in running water, and cutting by the celloidin-method. Sections should be cut longitudinally and transversely. The early changes in the axis-cylinder and myelin-sheath are beautifully shown, and even single degenerated fibres can be followed the whole length of the spinal cord. The healthy fibres are stained a light greenish gray, but both the axis-cylinder process and breaking-up myelin are stained *black*, owing to fatty degeneration.

This method is most suitable for *early* degenerations one week to one month after the lesion. For *later* degenerations, the Weigert or Weigert-Pal methods are most suitable. When sclerosis has taken place, it is better to adopt one of the latter methods; the healthy white matter is then stained blue, and the *sclerosed* tissue is yellow or unstained, according to the method adopted. Wallerian degeneration of the nerve-fibres of the central nervous system must occur in all organic lesions, and its extent and distribution will depend entirely upon the ganglion-cells destroyed, or upon the fibres which have been interrupted in their continuity with the cells of which they are the outgrowths.

The microscopical changes in the fibres, as a result of degeneration, are a breaking-up of the myelin-sheath (there is no neurilemma), an alteration in its chemical composition, and swelling of the axis-cylinder-

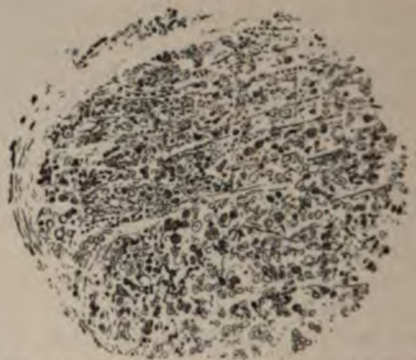
FIG. 309.



Section of the lumbar enlargement of spinal cord of monkey. Showing degeneration in the posterior column on one side, the result of section of the first sacral posterior root. It will be observed that all the short spinal root-fibres show no degeneration, these having already formed their end station at a lower level. The black tract near the middle line consists of two sets of medium length, which end about Clarke's column, conducting cerebellar impulses and long fibres which pass all the way up the cord in Goll's column to end in the funiculus gracilis. Observe that the degeneration is strictly limited to the posterior column of the same side.

process owing to a fatty degeneration; the clear distinction between the central axis-cylinder and surrounding myelin thus being lost. Later, as the altered myelin is carried away by phagocytes, spaces may be seen with the swollen axis-cylinder in the middle; or empty spaces in the neuroglia-tissue occur owing to rupture and absorption of the degenerated axis-cylinder processes (Figs. 310 and 311). As the atrophy of the nervous structures proceeds, there is a hyperplasia of the neuroglia and proliferation of the glia-cells. The process during the early stages has been one of softening; it is now a true **sclerosis** with shrinking, but there is no tendency (in uncomplicated *primary* or *secondary* systemic

FIG. 310.



Degeneration of crossed pyramidal tract at the tenth dorsal segment, forty days after hemisection of the spinal cord in the mid-dorsal region. The drawing was made from a photo-micrograph of a section of the posterior part of the lateral column, stained by the Pal method. The condition is one of commencing sclerosis. The black dots are the swollen axis-cylinder processes, mingled with the degenerated myelin; here and there are parts unstained, showing that the nerve-fibres have disappeared and neuroglia alone is left. A few empty spaces are seen scattered about, showing the previous existence of nerve-fibres at these points. A large number of healthy fibres are seen mingled with the degenerated fibres; these are the fibres of the direct cerebellar tract on their way to the periphery of the cord. (Mott, *Phila. Trans.*, 1892.)

degeneration) for the sclerosis to extend its limits, and it may even be limited to a microscopic transverse area. Eventually a cicatricial tissue may be formed; and the presence of this impenetrable tissue may be

FIG. 311.

Degeneration of crossed pyramidal tract at the eighth dorsal segment, seventy days after hemisection of the spinal cord in the mid-dorsal region. Prepared and drawn in the same way as Fig. 310. Much more *sclerosis* and *atrophy* are seen. The degenerated nerves have for the most part disappeared, empty spaces in the neuroglia being left; some few black dots are shown—indications remaining of degenerated nerve-fibres. At the periphery the healthy fibres of the direct cerebellar tract are seen. (Mott, *Phila. Trans.*, 1892.)

the reason why in the higher animals there exists no definite proof that *regeneration* of nerve-fibres can take place in the central nervous system.

The Chemistry of Degeneration.—The nervous system is composed chemically of very complex bodies, *e. g.*, *proteids*, *nucleoproteids*, *neurokeratin*, and *protagon* or *lecithin*, which forms the principal constituent of the myelin-sheath. This is a complex *phosphoretted fat* which stains black with osmic acid like all other forms of fat; but the myelin-sheath differs from tissues containing ordinary fat, such as olein, palmitin, stearin, by the fact that when white nervous matter is placed for some time in Müller's fluid the constituent myelin no longer stains black with osmic acid, but an ashy gray. This difference in chemical reaction is the basis of the Marchi method. It is probable that the chemical decomposition which occurs when myelin undergoes degeneration is a breaking-up of the complex molecule of protagon (lecithin) thus:

$$\underset{\text{(lecithin)}}{C_{44}H_{90}NPO_9} + \underset{\text{(water)}}{3H_2O} = \underset{\text{(stearic acid)}}{2C_{18}H_{36}O_2} + \underset{\text{(glycero-phosphoric acid)}}{C_3H_9PO_6} + \underset{\text{(cholin)}}{C_5H_{15}NO_2}$$

For if a spinal cord which shows well-marked degeneration on one side be divided longitudinally into two halves, and each half dried, weighed, and the fat of each separately extracted with ether, it will be found that while on the degenerated side there is an increase of ether-extract (fat) as compared with the healthy side, there is less phosphorus, the presumption being that the above decomposition has taken place. Examination of the sections stained by the Marchi method shows that not only does the myelin-sheath stain black, but the axis-cylinder-process as well; the proteid matter has therefore undergone fatty degeneration; moreover, chemical analysis shows that this is so, for the degenerated half of the cord yields less proteid residue than the healthy half. It has been shown (Halliburton and Mott) that cholin exists in the cerebrospinal fluid of patients suffering with extensive degeneration of the nervous system, *e. g.*, general paralysis, and that it does not exist in the normal fluid. The existence of *cholin* in the cerebrospinal fluid of general paralytics renders it probable that auto-intoxication may occur in extensive degenerative processes of the nervous system. The action of cholin is to produce a fall in the blood-pressure, partly by its effect on the heart, but mainly by dilating the splanchnic arteries, owing to a toxic influence on the peripheral neuro-muscular mechanism. *Neurin*, a product of the decomposition of *cholin* by micro-organisms is a very powerful poison; it produces a preliminary fall, and then a rise, of blood-pressure with respiratory convulsions. These two bodies belong to the same group, chemically, as *muscarin*.

Effects of Degeneration upon Function.—The most important phenomena resulting from morbid changes affecting the nervous system are related to disturbances of the sensori-motor mechanism.

Paralysis.—There are two types of paralysis, according to whether a lesion affects the *upper corticospinal motor* neuron, or the *lower spino-muscular* neuron. *Paralysis of the corticospinal type* is met with in

brain-disease producing hemiplegia; it also occurs in both lower limbs after a transverse lesion of the cord, as in caries of the spine, tumors, focal myelitis; also in primary lateral sclerosis. If a transverse lesion exists in the cervical region, the arms are also affected. The characteristics of this form of paralysis are complete or partial loss of volitional power, with stiffness and rigidity of the limbs. The muscles are not wasted except from disuse, the deep reflexes are exaggerated, and there is no alteration in the electrical reaction of the muscle. *Paralysis of the spinomuscular type* is due to a morbid process affecting the motor neurons in the anterior horn, or their homologues (the nuclei of the motor cranial nerves) in the medulla and pons, or the nerve-trunks containing the axons of the neurons. It occurs in infantile paralysis, acute and chronic poliomyelitis, myelitis, progressive muscular atrophy, bulbar paralysis, syringomyelia, tumors and hemorrhages within the cord, medulla and pons, and softening of the cord from embolism and thrombosis. The characteristics of this form of paralysis are that the muscles affected are completely paralyzed, and that if they recover they do so imperfectly and slowly. Although all the muscles of a limb may be paralyzed, as a rule certain groups suffer particularly. The limb is not rigid, the muscles being relaxed and flabby and the articular surfaces of the joints no longer held in close approximation. The deep reflexes are lost completely. The muscles rapidly atrophy and upon electrical examination there is an early appearance of the reaction of degeneration. Sensory disturbances do not necessarily accompany this form of paralysis. Vasomotor disturbances are manifested by coldness and blueness of the limb. Fibrillary twitchings are very characteristic of this neuromuscular degenerative process.

Disturbance of Reflex Action.—The reflex acts are: (1) tendon or deep reflexes; (2) skin or superficial reflexes; (3) reflex functions of the bladder and rectum. Such reflexes may be increased, diminished, or lost.

The knee-jerk is the best example of a so-called deep reflex, but although dependent upon the integrity of the reflex arc of the fourth and third lumbar segments of the spinal cord, yet careful time-measurements have shown that it is not a true reflex. It is produced by striking the quadriceps tendon *put on the stretch* by flexing the knee; the hamstring muscles are thus at the same time relaxed, so that the action exerted by them in antagonism to the quadriceps (Sherrington) is done away with. This is not, however, so much due to the fact that relaxation of the flexor muscles of the knee leaves that joint more free to move when the quadriceps extensor is excited to contraction by tapping its stretched tendon, as to the removal of an antagonistic tonic influence through afferent nerves (fifth and sixth lumbar roots) which the flexor group of muscles exert through the spinal reflex arc upon the correlated extensor group (Fig. 312). Absence of the tendon-reflex without wasting and degeneration of muscle, indicates degeneration of the posterior column of the cord. Absence of the tendon-reflex with wasting of muscle and sensory disturbance, indicates peripheral nerve degeneration or destruction of the central gray matter of the anterior and po-

terior horns. Absence of the tendon-reflex with wasting and degeneration of muscle, but without sensory disturbance, indicates degeneration of the anterior horn cells or primary progressive myopathy.

By muscular degeneration is not meant disuse-atrophy, but a wasting accompanied by changes in electrical excitability of the nerve and muscle. Bastian has pointed out that complete destructive transverse lesions of the spinal cord high up in the dorsal or cervical regions (in which *presumably the reflex arc is intact*) are often followed by absence of the knee-jerk. Of course, the pyramidal tracts will be degenerated, and it is difficult, therefore, to understand why the knee-jerks are lost.

FIG. 312.

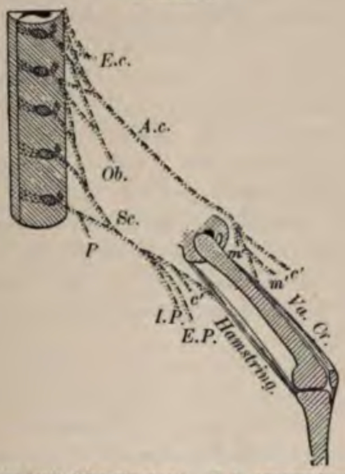


Diagram to explain the knee-jerk (Sherrington). *E. c.*, external cutaneous nerve; *A. c.*, anterior crural nerve with *c'*, cutaneous, and *m'*, muscular branches, coming from the third and fourth lumbar segments of the spinal cord; *Ob.*, obturator; *Sc.*, sciatic nerve with *I. P.*, internal popliteal, *E. P.*, external popliteal branches; *Va. Cr.*, the vasti and crureus muscles, the internal portion being especially concerned in the knee-jerk. Destruction of the reflex arc of the third and fourth lumbar segments in either its efferent or afferent portions will abolish the knee-jerk, because it will either paralyze the vastus crureus muscle or destroy its "myotatic" irritability.*

It has been thought by Bastian to be due to the removal of cerebellar influence. The knee-jerk is diminished in old age, during sleep, and in anæmia of the spinal cord.

In cases where the knee-jerk is exaggerated owing to removal of cortical influence by degeneration of the pyramidal tracts, another phenomenon is often obtainable; if the calf-muscles which extend the ankle-joint are suddenly put on the stretch by pressing the hand against the sole of the foot, a quick contraction occurs, and by keeping up the pressure there is a recurrence of the contractions at a regular

* *Myotatic irritability* is the term used by Gowers to embody his view that the knee-jerk and other deep reflexes depend on the increased irritability of a *stretched* muscle. If the tension is sudden and forcible, not only increased irritability, but also visible contraction occurs. This is especially evident when cerebral influence has been removed by pyramidal degeneration.

rate (about eight per second); the foot is thus thrown into a series of clonic spasmodic contractions termed the *foot-clonus* or *ankle-clonus*. Conditions which give rise to ankle-clonus are usually accompanied or followed by *contracture*, a state of permanently increased muscular tonus.

The superficial skin-reflexes, *epigastric, gluteal, cremasteric, plantar*, are usually lost in those diseases of the spinal cord in which the tendon-reflexes are exaggerated. They are frequently lost in organic brain diseases, in which the tendon-reflexes are also exaggerated. In functional conditions, such as hysteria, in which the deep reflexes may be exaggerated, they are not lost. In diseases in which the lateral columns of the spinal cord undergo degeneration, a peculiar modification of the plantar reflex may occur, characterized by contraction of the extensor muscles of the toes (*extensor response, Babinski's sign*).

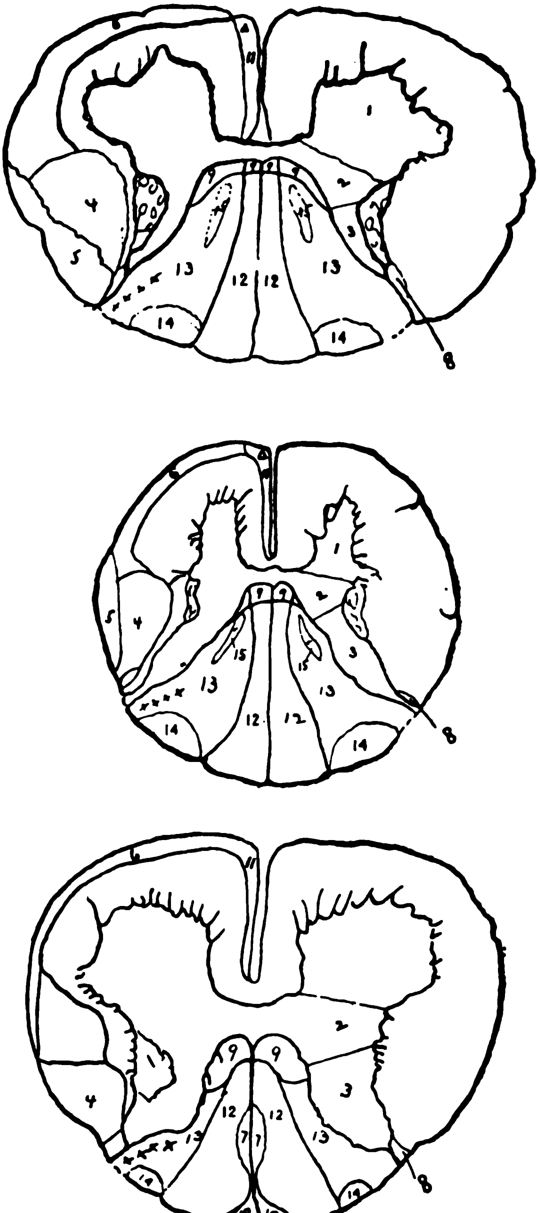
Examples of *reflex spinal tonus* are also afforded by the action of the sphincters of the bladder and rectum. The tonic contraction of these muscles is abolished by destruction of the lumbar enlargement of the spinal cord—hence the resulting incontinence of fæces and of urine. If, on the other hand, a transverse lesion of the spinal cord be present above the lumbar enlargement, no loss of these reflexes will occur; but in the absence of volitional impulses from the brain, the sphincter of the bladder may remain contracted, impeding the outflow of urine, and dilatation of the bladder will ensue as the urine accumulates; this dilatation may produce a secondary incontinence as the sphincter finally undergoes stretching.

Disturbance of Sensation.—Irritation of the sensory areas of the cord may cause *hyperæsthesia*—an excessive sensibility of the skin to ordinary stimulation; or *paræsthesia*, viz., burning, tingling, creeping, and numbness, *referred* to particular parts of the skin and limbs which correspond to the segments of the cord irritated. Pressure on nerve-roots also gives rise to very severe localized pain; and at the level of a focal lesion of the cord, as in transverse myelitis, there is a feeling as of a cord round the waist (*girdle sensation*).

Destruction of the sensory tracts of the spinal cord or of the posterior spinal roots will lead to loss of sensation. The sensory defects may be loss of sensation (1) of touch (*tactile anæsthesia*), (2) of painful sensations (*analgesia*), (3) of heat and cold (*thermo-anæsthesia*), (4) of muscular sense (*ataxia*).

The posterior roots convey to the cord all forms of sensibility; hence when the morbid process affects the roots all forms of sensibility may be affected; but when the fibres forming the roots enter the cord, they separate morphologically into three systems having different functions: (1) "short spinal," ending in the gray matter of the spinal segment, taking part in the reflex arc; (2) "middle length" fibres, which pass into the external part of the posterior column and conduct impulses to the cerebellum; (3) "long fibres," which at first lie in the external portion of the posterior column, afterward reach the median portion, and conduct kinæsthetic impulses to the opposite cerebral hemisphere. Hence it is possible, as in diseases of the spinal cord, for one form of sensation to be lost while others are preserved. Thus in diseases of

FIG. 313.



anterior horn; 2, base of anterior horn; 3, posterior horn; 4, pyramidal tract; 5, direct cerebellar tract; 6, anterolateral tract; 7, oval area of Flechsig; 8, Lissauer's zone; 9, cornu commissural; 10, Gombault and Philippe's tract; 11, direct pyramidal tract; 12, Goll's column; 13, Burdach's column; 14, postero-internal triangle; 15, comma tract; x x x x, root zone. 7, 9, 10, and 15, are endogenous tracts, and do not undergo degeneration in locomotor ataxy. The ground fibres situated around the gray matter are commissural, uniting the different segments of the cord.

the *gray matter* (syringomyelia), we have the characteristic symptoms of *sensory dissociation*, viz., tactile sense preserved, while sense of pain and of heat and cold is lost. In diseases of the posterior columns, *e.g.*, locomotor ataxy, we may have ataxy either alone or associated with anæsthesia. In general myelitis all the sensory tracts are implicated, and all forms of sensation are affected. In transverse lesions of the cord there is an interruption to the transmission of all forms of sensation below the lesion.

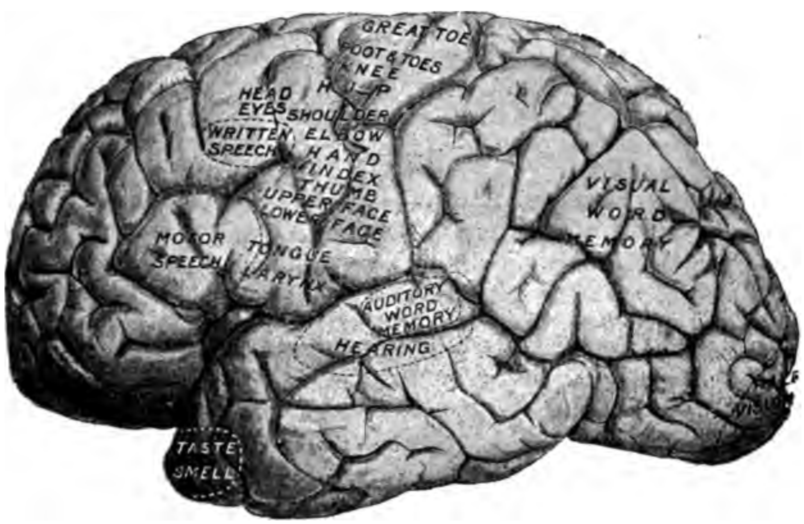
The spinal cord has two sets of functions: (1) the direct reflex control of definite visceral and somatic regions of the body, by means of its thirty-one pairs of segment nerves, (2) the functional of transmitting sensory afferent impulses to the brain and motor impulses from the brain. The path of the motor impulses from the brain is well known. The path of the sensory afferent impulses is not so definite. It may, however, be concluded that the gray matter conducts painful and thermal sensations, while the posterior columns conduct tactile and muscular sense-impressions. The other afferent tracts in the cord are the anterolateral (ventral cerebellar) and the direct cerebellar; they conduct impulses to the cerebellum. There is a descending cerebellar tract, occupying the anterior border of the lateral column, the fibres of which probably arise from Deiters's nucleus (Fig. 333). The accompanying diagram (Fig. 313) represents the various afferent and efferent tracts of the spinal cord. Those tracts which arise from cells within the spinal cord are spoken of as *endogenous*, those which arise from cells outside—*e. g.*, the spinal ganglia, are spoken of as *exogenous*.

The principal symptoms of disease of the spinal cord are, (1) paralysis, (2) changes in reflex activity, (3) alterations of gait and posture, (4) disturbance in the control of the sphincters of the bowel and bladder, (5) sensory defects, (6) sensory incoördination, "ataxy," (7) trophic disturbances. The symptoms arising from disease of the medulla and pons are especially related to *affection of the nuclei of the cranial nerves, combined with interruption of the motor and sensory tracts.* Owing to the existence of so many important structures close together, small vascular lesions or tumors in these regions produce serious and generally fatal consequences.

Cerebral Localization.—In the brain, differentiation of function and structure finds its highest development, and morbid processes may be so localized as to lead to derangement or loss of some particular function. It may not be out of place, therefore, to give a brief account of the functions of the brain so far as the localization of disease is concerned. Cerebral localization in *man* is sometimes said to have had its foundation in the discovery, in 1861, of the *speech-centre* by Broca, after whom is named that portion of the brain corresponding to the *third left frontal convolution, and its junction with the ascending frontal.* The important clinical observation of Hughlings Jackson, who showed that an irritative lesion of the cortex produced epileptiform convulsions affecting representative groups of muscles in a definite march, received its anatomical and physiological explanation by the experimental discovery of cerebral

localization by Fritsch and Hitzig in the dog. Various *monoplegias* in man due to localized lesions have been noted, by which the *Rolandic area* has been mapped out into definite regions, closely corresponding to those mapped out by stimulation in the orang-utan by Horsley and Beevor (Fig. 314). Munk first demonstrated experimentally that removal of both *occipital lobes* caused *blindness*, and that removal of one caused blindness of the opposite half of the field of vision (*hemianopsy*). There are, however, functions of the human brain which can only be ascertained by association of defects observed during life with lesions found after death. Thus have been identified

FIG. 314.



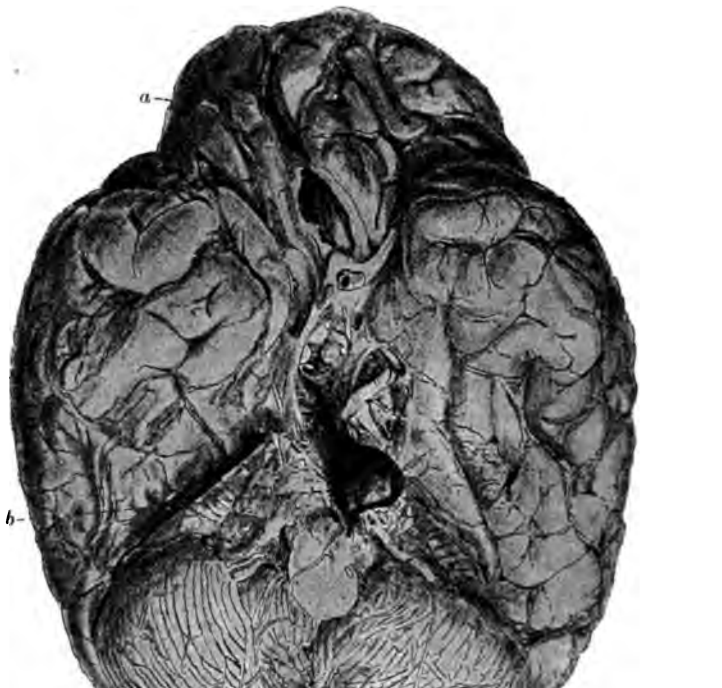
Left hemisphere, showing the situation of the cortical projection-centres. The parts which are not lettered represent Flechsig's association-centres.

the centres connected with (1) *articulate speech, absence of which is termed motor aphasia, localized in Broca's convolution;* (2) *visual word memory, localized in the angular gyrus;* (3) *auditory word memory*—cases of softening of the *posterior third of the first temporal convolution* having been observed in persons who could read written language, but could not understand spoken language; (4) cases of disease of the *base of the second frontal convolution* found associated with *inability to write words*, but not inability of utterance (*agraphia*). According to Flechsig, certain areas of the cortex contain only neurons of association and no neurons of afferent or efferent projection; these latter are found, according to him, only in the excitomotor (Rolandic) region of the cortex and those regions which are concerned with special sense, *e. g.*, occipital lobes and tip of the temporosphenoidal lobe; *all the remainder of the cortex consists of association-centres.* It is probable, from observations upon the effects of disease as well as of extensive injuries, that the *frontal lobes* are concerned with the *higher functions of mind,* as impairment of the moral and emotional faculties has been the

only result of extensive destruction of the cortex in this region. There is abundant evidence to prove that the departure-platform of the efferent motor projection system is in the central convolutions (Fig. 314). The neurons of this system are physiologically connected by the dendrons with the terminals of the afferent projection system, and by the tangential system of fibres of the superficial layers of neurons, by which co-ordinate action of adjacent systems is maintained.

In every voluntary movement the whole *three nervous circles* (*cerebral, cerebellar*, and *spinal*) are in action (Fig. 333); impulses are ascending

FIG. 315.



Photograph of base of brain. *a*, atrophy of the right frontal lobe, due to softening; *b*, healed aneurism of the basilar artery; from a case of post-hemiplegic dementia with epilepsy.

the afferent systems and descending the efferent during the whole time. We are conscious of the position of our limbs by the sensations which ascend the afferent system, and this consciousness is necessary to, and precedes, volitional movement. *The sense of movement* (*kinæsthesia*) is a combination of the sensations proceeding from skin, muscle, tendons, and joints. *A priori* we should expect the arrival-platform of these sensations in the cortex to be in close proximity to the departure-platform of the efferent system. Flechsig, by the embryological method, has

shown that the sensory fibres of the internal capsule terminate in the central convolution. It must be admitted, however, that *lesions of the cortex do not as a rule produce marked sensory defects.*

Lesions of the brain *may be irritative or destructive.* If an *irritative lesion* be situated in the *excitomotor area* it will cause *fits*, commencing usually with a *sensory aura* in the part which is thrown into convulsions. If it be a *destructive lesion*, there will be a *loss of function*, which may or may not be discoverable, according to the side of the brain affected and its seat. *Loss of speech*, of *visual word-memory*, of *auditory word-memory*, or *agraphia*, only occur when the centres in the *left hemisphere* are destroyed, *unless* the patient be born a *left-handed person.* Extensive lesions in some portions of the brain, *e. g.*, frontal region, may not be discoverable during life, but probably this is owing to our want of discernment and of previous knowledge of the intellectual and moral character of the individual before he was afflicted. Vascular lesions may affect extensive areas of the brain simultaneously. Thus, if the *middle cerebral* artery be blocked at its commencement, there will not only be *softening of the whole cortical area* supplied by this vessel, but

FIG. 316.

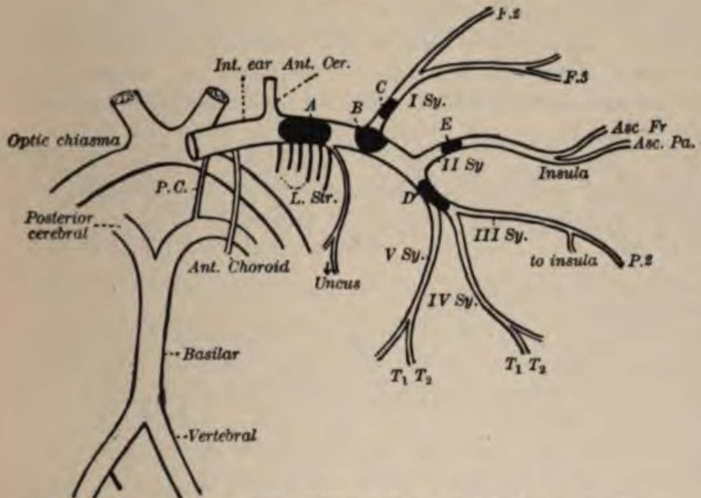


Diagram after Von Monakow to show the effect of embolism. See text.

also of *the internal capsule and basal ganglia* (A, Fig. 316), resulting in *hemiplegia;* and, if on the *left side*, there will be *aphasia*, *word-deafness*, and *word-blindness.* If the artery be blocked at B beyond the basal arteries, there is a possibility of some collateral circulation being restored by the anterior cerebral. If the *first* Sylvian branch is blocked (C), there will be *softening* in *Broca's convolution and aphasia;* if the *second* (E), there will be *softening of the Rolandic area* and *hemiplegia;* while blocking of the *posterior main division* (D) of the middle cerebral artery on the left side will cause *word-blindness* and *word-deafness*, frequently accompanied by dementia, but not by motor aphasia or hemiplegia. The effect

of occlusion of the *posterior cerebral artery* is lateral homonymous *hemianopsy*, often only partial in character.

Lesions in the *centrum ovale* produce effects according to the size and seat of the lesion. The motor and sensory projection-systems form two funnels with their base at the cortex and their neck at the internal capsule. It requires a large lesion in the region mentioned to interrupt the whole of the fibres belonging to one of these systems.

Lesions of the *internal capsule* are especially common in both softening and hemorrhage. Both motor and sensory fibres pass through this region, the latter occupying the posterior third of the capsule, the former the central third, while the functions of the anterior fibres are uncertain. The most common effect of a lesion in this region—or of one which causes pressure upon the capsule—is *hemiplegia*, the opposite side of the body being paralyzed. This condition may be accompanied by *hemianæsthesia*, in some cases, on the same side of the body as the paralysis. The functions of the *cerebellum* have been determined more accurately in recent years, and Luciani has shown that removal of this organ in animals produces *asthenia*, *atonia*, and *astasia*. It is generally admitted that the cerebellum is an organ concerned with *muscular coördination*, and it is probably by the exercise of this function under the guidance of peripheral stimulation that it serves to maintain *steadiness in gait and station*. Each lateral lobe of the cerebellum is connected with the motor cortex of the opposite cerebral hemisphere. Probably the cerebellum has also an important influence upon the *maintenance of tonus* in the *fixation of a joint* by the *correlative action* of the antagonistic muscles. The results of *cerebellar disease*, *e. g.*, tumor, cyst, or abscess, are *unsteadiness of gait and station;* the ataxy which results is peculiar, *the gait being oscillating*, causing the patient to sway to and fro like a drunken man. As a rule, the patient walks and tends to *fall toward the affected side in unilateral lesions*. There is generally *hemiparesis* on the same side as the lesion.

Injury to the *pons varolii* may be accompanied by hyperpyrexia, by conjugate deviation of the head and eyes, by contraction of the pupils, and by crossed paralysis, the face being paralyzed on the same side as the lesion, the arm and leg on the opposite side. This last phenomenon is due to the fact that the fibres from the face-area of the cortex cross to the opposite side in the pons; those from the arm- and leg-areas decussate in the medulla.

INFLAMMATION OF THE MENINGES.

Three membranes enclose the central nervous system, but owing to the intimate connection of the pia mater and arachnoid these always suffer together. Inflammation of the tough fibrous *dura mater* is termed *pachymeningitis*. Inflammation of the soft *pia-arachnoid* is termed *meningitis*, or more precisely, as the antithesis to pachymeningitis, *leptomeningitis*.

Pachymeningitis.

The dura mater consists of two layers, a thick outer layer which is periosteal in its functions, and a thin inner layer with a smooth epithelial surface. Either layer may be the seat of inflammation, which is usually chronic.

External pachymeningitis is frequently caused by caries or necrosis of the spine and bones of the skull due to syphilis, wounds, or extension from disease of the middle ear.

Morbid Anatomy.—The dura mater at first is œdematous and congested; later it may be covered with pus, which separates it from the bone and also infiltrates its substance. If the inflammation does not become purulent, the thickened outer layer of dura mater may become firmly adherent to the bone.

Internal pachymeningitis is characterized by the formation of a false membrane, usually very vascular and consisting of several layers. Owing to the rupture of vessels, blood-cysts are found between the layers, known by the name of *hæmatomata* of the dura mater. The *false membrane*, which usually causes adherence of the dura mater to the arachnoid, extends generally over the greater part of one or both hemispheres. The condition is rare, and met with usually in general paralysis of the insane and in chronic alcoholism.

Meningitis or Leptomeningitis.

Inflammation of the pia-arachnoid is in nearly all cases due to infective inflammation produced by micro-organisms. The most important form is tubercular (p. 372). A number of other causes of infection exist, which may be considered under the headings *local* and *general.*

Local.—(1) Traumatic injuries of the head with direct infection.

(2) Adjacent disease outside the dura mater, suppurative otitis, chronic ear-disease with caries of the mastoid or petrous portions of the temporal bone, and occasionally disease of the bones of the nose or orbit. The infection in these cases may spread directly, or along the course of lymphatics or bloodvessels. It is probable that some cases of meningitis in which no visible organic cause is found post mortem may have arisen by the infection gaining access to the middle ear by the Eustachian tubes.

(3) Tumors and abscesses of the brain may cause inflammation of the adjacent meninges.

General.—Meningitis may occur in the course of certain infective diseases—*e. g.*, smallpox, scarlet fever, measles, septicæmia—and in syphilis, gonorrhœa, pneumonia, and acute rheumatism. Cerebrospinal meningitis, due to a specific diplococcus (p. 313), may also occur in an *epidemic form.* A form of meningitis described by Barlow and Gee, designated *posterior basic meningitis*, is also due to the same diplococcus. It affects infants and young children, and one-half the

cases are fatal. Meningitis in rare instances has followed a blow not causing any wound, and it has been found post mortem in some cases of sunstroke. Thickening and opacity of the membranes also occur in chronic wasting degenerative processes of the central nervous system; for example, tabes dorsalis and general paralysis. The process is here generally considered to be *secondary* to the atrophy.

Morbid Anatomy.—When the infection is local the meningitis may be circumscribed, but when the cause is some infective blood condition it is usually generalized, and may in some cases affect the spinal as well as the cerebral meninges—*e. g.*, meningitis occurring in the course of pneumonia may in many ways resemble the epidemic form. Tubercular meningitis usually affects *the base* primarily and especially, whereas in other forms the *convexities* of the hemispheres are affected. Certain changes are common to all forms of meningitis. The pia mater is intensely hyperæmic and red, as if the vessels had been artificially injected. Soon opacity and thickening of the membranes occur, recognizable most readily in the arachnoid; and along the course of the vessels there is an opacity owing to distention of the perivascular lymphatic sheaths. An inflammatory exudation from the bloodvessels of the pia mater occurs; this may be serous, seropurulent, or purulent, and is manifest especially over the sulci of the convexity and in the spaces at the base of the brain. In severe cases pus mixed with fibrin forms a continuous opaque yellowish layer under the visceral layer of the arachnoid. The inflammation usually spreads to the adjacent structures, causing neuritis, myelitis, encephalitis, and, later on, adhesions. The ventricles of the brain and the interpeduncular subarachnoid space may be distended with a turbid serous fluid, and the choroid plexus as well as the velum interpositum is usually congested and swollen. This fluid, examined microscopically, may be found to contain large granular epithelial cells, leucocytes, or pus-cells.

The suppurative process is extremely marked, and often very rapid in formation in epidemic cerebrospinal meningitis.

Effects.—The first stage, or *period of excitation*, is characterized by *headache*, *delirium*, *rigidity*, and *general or local convulsions:* these symptoms can be accounted for by the irritation, in early stages of inflammation, of the cortex, crus, pons, medulla, or the spinal cord and nerves.

The second stage or *period of depression* occurs as the inflammation extends into the cortex and motor nerves, *paralyses* of various kinds appearing. In the final stage, the increasing effusion into the skull causes a rise of intracranial pressure, and thus induces *coma*.

THE CEREBROSPINAL FLUID.

The cerebrospinal fluid is altered in many cases of disease. Thus, it is *increased in quantity* in cases in which there is pressure on the veins of Galen and resulting venous hyperæmia, as well as in inflammatory conditions of the membranes.

Obliteration of the foramen of Magendie, by preventing the escape of cerebrospinal fluid from the ventricles of the brain and causing its accumulation in these cavities, produces hydrocephalus or distention of the ventricles with fluid (p. 559); the cerebral substance then atrophies as a result of pressure. In other cases wasting of the brain-substance is followed by increased exudation of fluid to fill up the cranial cavity (general paralysis, senile atrophy).

In meningitis the number of *leucocytes* in the cerebrospinal fluid is increased—in tuberculosis the lymphocytes predominating, in most other infective conditions the multinuclear leucocytes. *Infective organisms* may exist in this fluid; as, for example, tubercle-bacilli, pneumococci, meningococci, and trypanosomes. The cerebrospinal fluid may be obtained for examination by "lumbar puncture"—that is, by insertion of the needle of an exploring-syringe into the spinal theca in the region of the cauda equina.

INFLAMMATION OF THE CENTRAL NERVOUS SYSTEM.

Encephalitis.—Inflammation of the brain may arise from three causes: traumatic injury, inflammation of adjacent structures, and acute infective diseases—erysipelas, typhoid fever, typhus and diphtheria. Strümpell considers that infantile cerebral hemiplegia is due to a primary systemic inflammation of the gray matter of the motor cortex, analogous to anterior poliomyelitis; hence he terms it *polio-encephalitis.* Very probably the two diseases have an identical cause. *Anatomically,* the alteration in the brain-tissue which results from acute inflammation is a process of *red softening.*

Cerebral Abscess.—The causes may be divided into local and distant. By far the most frequent *local* cause of cerebral abscess is *chronic ear-disease.* Inflammation of the middle ear or mastoid cells is often followed by a purulent discharge and *caries of the bone;* not infrequently arrest of the discharge is followed by abscess. Occasionally there may be no bone disease, only suppurative inflammation of the middle ear or mastoid cells; and in such cases the infection probably passes by the perivascular lymphatics along the veins which connect the tympanic cavity and mastoid cells respectively with the superior petrosal and lateral sinuses. Disease of the nose and orbit, syphilitic caries of other bones, tumor of the brain, and injury are among the rarer causes of cerebral abscess. *Distant causes* are pyæmia, gangrene of the lung, fœtid bronchitis, bronchiectasis, and empyema—all rarely met with.

Morbid Anatomy.—Abscesses are usually solitary, but there may be several, and in pyæmia sometimes many; in size they are rarely less than that of a walnut, and many even involve the greater part of a cerebral hemisphere. Owing to the frequency with which ear disease acts as a cause, abscess is met with most often in the temporosphenoidal lobe and the lateral lobe of the cerebellum. In nasal and orbital disease it is usually found in the adjacent frontal lobes. In chronic

cases the abscess cavity is limited by a well-defined capsule: the more acute the abscess the less is there a tendency for it to be circumscribed.

The process of *suppuration* commences with inflammatory softening; cell-infiltration replacing and destroying the normal structure. Pus is formed which, in the case of ear disease, is usually of a greenish color and frequently of fœtid odor and acid reaction. It is made up of pus-corpuscles, degenerated cells, fat, cholesterin, hæmatoidin, and micro-organisms, usually staphylococci and streptococci. The pus is contained at first in an irregular cavity, and there is a tendency for the abscess to increase by a necrosis of portions of the limiting tissue; it may thus, by spreading, burst into the lateral ventricles or externally. It may, however, become encapsuled by connective tissue, and the pus, undergoing mucous degeneration, becomes thick and viscid. It is thought that pus thus encapsuled may dry up and caseate or calcify, or even be completely absorbed, leaving little more than a scar. The symptoms produced by abscess depend upon local irritative effects of the infective inflammation, septic absorption, and, in severe cases, intracranial pressure.

Myelitis.—The term *myelitis* has been used for all forms of degeneration of the spinal cord, and thus we have the subdivisions acute, subacute, and chronic; or it may be considered according to its localization, and then the terms transverse myelitis, diffuse myelitis, leucomyelitis, poliomyelitis, and meningomyelitis are used.

The true causes are probably infective organisms or toxic agencies. Cold and injury may operate, as in pneumonia, by lowering the vital resistance. Some forms may be due to vascular occlusion, and analogous to cerebral softening.

Of all the infective diseases which lead to these various forms of myelitis, syphilis is the most important; but tuberculosis (in the production of Pott's disease and meningomyelitis), epidemic cerebrospinal meningitis, gonorrhœa, measles, diphtheria, influenza, scarlet fever, smallpox, and typhoid fever offer examples of infective diseases which have been followed by various forms of myelitis. Probably the inflammation is due to the *toxins* produced in the blood by the infective organisms. Other toxic agencies, as in ergotism, pellagra, and lathyrism,[1] offer examples of *vegetable poisons;* lead and arsenic, of *mineral poisons*, any of which may cause myelitis.

Acute Myelitis.—The naked-eye appearances are variable: the spinal tissue is sometimes softened, pinkish-white in appearance, yellowish or brownish-red, according to the condition of the bloodvessels and the amount and change in the extravasated red blood-corpuscles. In an early stage, a large number of granular corpuscles and amyloid bodies appear; the axis-cylinders are either swollen and granular, or destroyed, and the myelin-sheaths of the white matter are rapidly broken up. The ganglion-cells undergo degeneration; their processes are swollen and varicose, or broken off (Fig. 319). Stained by Nissl's method, the chromatic substance loses its normal appearance, and the granules are

[1] Poisoning by *Lathyrus*, chickpea.

no longer visible in the cell-body or dendrons. The protoplasm is diffusely stained, and the nucleus eccentric or extruded; later the cells present signs of atrophy, and eventually may completely disappear.

The *vessels*, thrombosis of which appears in many cases to be the determining cause of the above-mentioned changes, are engorged with blood, and their lymphatic sheaths filled with leucocytes; and when the inflammation is very intense hemorrhages may be found. There is an increase of nuclei and small round cells in the gray matter, and Deiters's cells are more numerous than normal.

Later the connective tissue undergoes proliferation, and there is rapid progressive softening of the nervous elements owing to granulofatty degeneration. The process thus passes into the chronic stage, constituting *gray softening*. Hemorrhages may occur in these foci of softening, and eventually the process ends in a *sclerosis*, an overgrowth of fibrous connective tissue replacing the cells which have been destroyed.

All varieties of **diffuse myelitis** have a common pathological anatomy, but the clinical symptoms will of necessity vary according to the seat, extent, and distribution of the inflammatory process.

Periependymal, or central, myelitis occasionally occurs, but the effects depend, as in syringomyelia, upon the amount and seat of the destruction of the gray matter.

Meningomyelitis.—Erb has called attention to the fact that in syphilis, very frequently in the early secondary stage of the disease, a *focal myelitis* occurs, the principal features of which are diffuse myelitis of the white matter (not involving definite tracts), local thickening of the meninges, and a *periphlebitis*, with venous stasis or thrombosis, but no syphilitic changes in the arteries.

Transverse myelitis is produced by Pott's disease, aneurysm, growths, and thickening of the dura mater. The symptoms vary according to the seat of the lesion. The mechanism of the damage to the cord is twofold—viz., *compression* and *inflammation*. The cord may (at the seat of compression) be flattened, indented, or even reduced very greatly in size (Fig. 337); on section it has usually a gray appearance. The microscopical appearances of inflammation correspond to those already described, and the changes in the cord above and below the seat of injury are described under *secondary degenerations*.

The pathological effects may be considered under two distinct headings—*root symptoms* and *cord symptoms*. The former usually develop first in the form of *shooting pains*, owing to irritation of the sensory roots involved. With the pain there is usually *hyperæsthesia* of the skin. Irritation of the motor roots causes *painful contracture*. *Cord symptoms* are: paresis or paralysis below the lesions, *increase* of *superficial reflexes* and of *myotatic irritability*. There may be no loss of sensibility discoverable in the parts below the lesion, although there is complete paralysis; but there may, on the other hand, be delay, and in severe cases absolute loss of sensation. Paralysis of the sphincters and a tendency to bedsores accompany lesions affecting the lumbar enlargement. If the lesion is in the lower cervical region, the pupils may be affected from

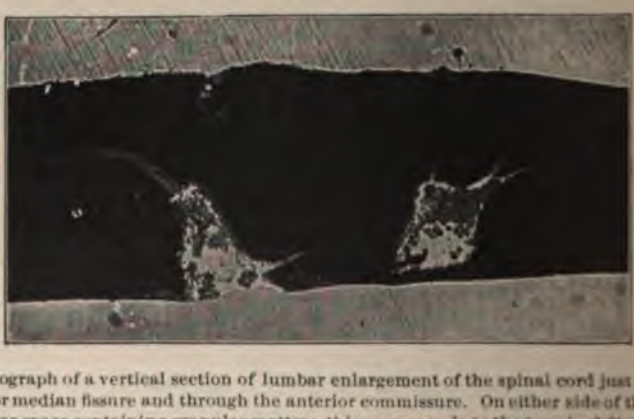
implication of the ciliospinal centre, and the pulse-rate diminished from damage of the accelerator fibres of the heart.

Poliomyelitis.—An acute inflammation of the anterior cornua is the morbid change found in *infantile paralysis* and in *acute spinal paralysis* of the adult. Singer and Munzer have shown that they can produce a destruction of the anterior horn cells of the rabbit by compression of the abdominal aorta, thus cutting off the supply of blood to the lower end of the cord. It is highly probable that anterior poliomyelitis is due to blocking of the anterior radicular arteries by inflammatory thrombosis, possibly of infective origin (Fig. 317), by which one or all the groups of cells in the anterior horn are destroyed, according to the extent of occlusion; thus patches of softening arise in the anterior cornua on one or both sides. The microscopical appearances of the anterior horns in a recent case are similar to those described as occurring in acute myelitis (Figs. 318, 319). The appearances presented by the spinal cord may vary very considerably according to the length of time which has elapsed since the onset of the disease. In an old case, the segments of the spinal cord corresponding to the muscular paralysis (usually lumbar and cervical en-

FIG. 317.

Diagrammatic representation of the supply of the groups of anterior horn cells by the radicular branches of the anterior median arteries. Showing one group of cells completely destroyed by occlusion of one of these small vessels, and thus explaining why in poliomyelitis there is usually permanent loss of movement in some one or more muscles.

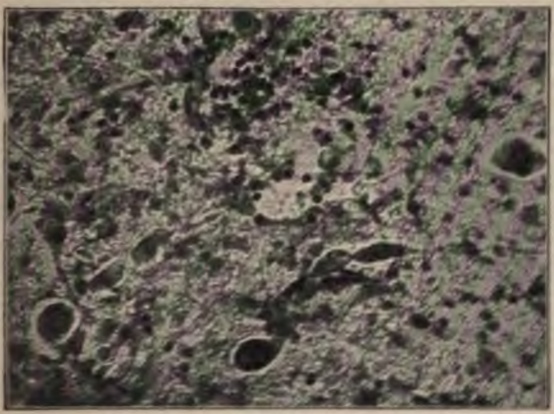
FIG. 318.



Photomicrograph of a vertical section of lumbar enlargement of the spinal cord just behind the anterior median fissure and through the anterior commissure. On either side of the mid-line is a clear space containing granular matter; this corresponds to the terminal distribution of one of the branches given off on either side by the anterior median artery at the bottom of the fissure. From a case of acute infantile poliomyelitis; death fourteen days after onset. × 12. (See *Archives of Neurology*, vol. I.)

largements) exhibit a more marked translucency of the gray matter of the anterior horns; and if limited to one side, as it often is, a diminution in size of the anterior horn as compared with the opposite healthy side. The anterior horn cells may be absent, or vestiges of degenerated ganglion-cells, in the form of obtuse or rounded protoplasmic bodies without processes, may be present. The fine nerve-plexus around the cells is either greatly diminished or completely absent, and only neuroglia and Deiters's cells may be visible. The vessels are thickened. When the lesion is bilateral, it is rarely symmetrical; more frequently it is unilateral, and it will then be observed that there is secondary atrophy of correlated structures of the same half of the cord—viz., of the posterior column, anterolateral column, and posterior horn; some ob-

Fig. 319.



Photomicrograph of base of anterior horn, showing cells with swollen varicose axis-cylinders and acute inflammation in the tissues around. From a case of acute infantile poliomyelitis, in which death occurred fourteen days after onset. Specimen stained by Nissl method. × 250. (*Archives of Neurology*, vol. i.)

servers have described atrophy of the corresponding motor convolutions of the brain. Atrophy of anterior root-fibres must occur. Atrophy of the bones has also been found.

Landry's paralysis (*acute ascending paralysis*): no definite lesion has been described; it may be due to the effects of a toxin acting upon the central or peripheral nervous system. *The absence of troubles of nutrition and sensibility* points to the poison acting, like curare, especially upon the motor tract, and serves to distinguish the disease from acute myelitis (p. 552).

CONGENITAL DEFECTS OF THE BRAIN.

Only those defects associated with Congenital Hemiplegia, Diplegia, Epilepsy, and Imbecility will be here described (p. 24).

Infantile paralysis of cerebral origin arises from a number of morbid conditions. Some are of vascular origin, some are due to inflammatory conditions, and some to arrested development.

Morbid Anatomy.—*Cysts, areas of sclerosis,* or *patches of softening* may be found, the result of embolism, thrombosis, or hemorrhage, usually meningeal. *Porencephalon* is generally congenital. It is a defect of the convolutions of variable extent, by which a cavity is formed, penetrating a variable distance into the hemisphere, sometimes as far as the ventricles. The meninges are intact and present neither thickenings nor adhesions; often the membranes are found adherent to the ependyma of the ventricles. The defect is generally limited to the area of some definite vascular supply. The convolutions around usually present a radiate appearance.

Atrophy and Sclerosis.—Groups of convolutions, an entire lobe, or the whole of a hemisphere may be wasted, and usually in such cases there is atrophy of the opposite half of the cerebellum. The membranes may appear normal; more often they are thickened and adherent. Sometimes there are little nodular projections all over the surface of the atrophied convolutions. Some of these cases may be the result of *polio-encephalitis,* others are due to thrombosis of veins. In both conditions multiple hemorrhages, atrophy of nervous tissue, and overgrowth of glia-tissue are found.

Mention may also be made of a severe form of infantile paralysis of cerebral origin, associated with blindness, which affects members of the same family. It has been termed by Sachs, who described its pathology, "amaurotic family idiocy." It is a good example of *hereditary failure of development* (*agenesis corticalis*).

TUMORS.

Etiology.—The cause of cerebral tumors is, as a rule, unknown, except those of syphilitic and tubercular[1] origin, and the different varieties of parasitic cysts. Many are secondary deposits from growths elsewhere, or commence in the enclosing and supporting tissues of mesoblastic origin. There are, however, a number of tumors, of which **glioma** is the commonest, which commence in epiblastic structures; and these, together with other primary forms, are due to developmental causes, as yet little understood. Cerebral tumor is not infrequent: according to Starr, it is the cause of death in one case out of every 120 examined upon the post-mortem table of hospitals. Tumor is met with most frequently in early and middle life; it is twice as frequent in males as in females, and of all the cases of cerebral tumor more than *one-half are tubercular.* Excepting syphilis and tuberculosis, the other forms of primary tumor may develop in apparently healthy persons, although frequently there is a history of a *blow on the head, or local injury.* It may be that the blow merely excites inflammatory change in the tissue around a growth which is more or less latent, *e. g.,* a tubercular deposit.

[1] Syphilitic and tubular masses are inflammatory in nature, and not tumors in the strict pathological sense of the term.

(1) **Gliomata** (p. 103).—These growths do not necessarily destroy the brain-substance, for frequently the nerve-fibres, being merely pushed aside, retain their conducting power (Fig. 322).

FIG. 320.

Drawing from photograph showing hemiatrophy of the left hemisphere, from a case of congenital hemiplegia with epilepsy and imbecility. There was also atrophy of the right half of the cerebellum. It will be observed that the bone is correspondingly thickened where the bone is atrophied. The lesion was probably primarily in the anterior part of the optic thalamus.

(2) **Sarcoma** (p. 116) seldom arises in the substance of the central nervous system, being of mesoblastic origin. Primary sarcoma commences in the fibrous structures of surrounding tissues, for example, in the pia-arachnoid membranes, in the dura mater, in the periosteum of the cranial bones and vertebræ, and in the bones themselves, especially of the base of the skull.

(3) *Gummata* (syphilis of the nervous system (p. 565).

(4) *Tubercular masses* (p. 350).—These tumors are most frequently met with, according to Gowers, in (1) the cerebellum, (2) the cortex, and (3) the pons. They occur especially in children, and frequently give rise to *hydrocephalus*.

(5) *Carcinoma* is nearly always secondary, and the primary growth is most frequently in the mammary gland; this form is multiple and grows rapidly.

(6) *Psammomata* (p. 108) as a rule do not produce symptoms of intracranial pressure, although they give rise to convulsions when pressing upon the central convolutions. Many of these may be seen upon the post-mortem table in cases which were classed as epileptic dements in the asylums. The tumors are circumscribed and indent, but do not infiltrate the subjacent brain tissue, and are therefore quite capable of removal (Fig. 321).

Parasitic cysts (echinococcus and cysticerci) (p. 246), *cholesteatomata*,

FIG. 321.

Fibro-endotheliomatous tumor growing from the dura mater pressing on the frontal convolutions; attended with no paralysis during life, nor were signs of intracranial pressure observed, probably owing to the very slow growth. Patient was subject to fits and was demented.

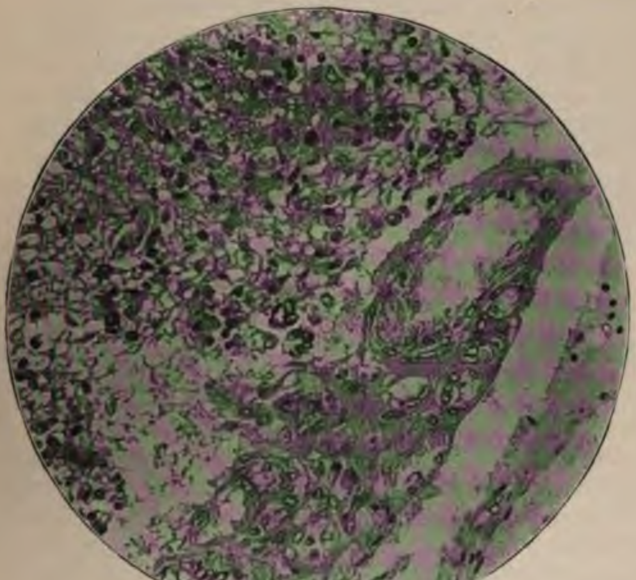
angiosarcomata, *angiomata*, *dermoid cysts*, *cysts of the choroid plexus*, and other growths—*e.g.*, *tumors of the hypophysis cerebri*—are in rare cases met with. The morbid anatomy of these tumors is described elsewhere.

The pathological effects of tumors are (1) *increased intracranial pressure upon all parts of the brain, producing compression of veins and hydrops ventriculorum;* and (2) *direct irritation or destruction of nerve-elements, causing loss or impairment of function.*

The **general symptoms of tumor** are *headache*, *vomiting*, *vertigo*, *slow*

pulse, *convulsions*, *stupor*, and *drowsiness*, and, most important of all as a means of diagnosis, *optic neuritis*. All these symptoms are probably due to increased intracranial pressure. *Optic neuritis* depends not so much upon the size and situation of the tumor, as upon the rapidity of its growth. There are three views as to the causation of optic neuritis, viz., (1) that it is due to irritation and inflammation of the sheath of the optic nerve, produced either by irritation arising from substances contained in the cerebrospinal fluid of the sheath of the optic nerve, or by direct extension of meningitis; (2) that it is due to obstruction of the outflow of the venous blood from the ophthalmic vein owing to the increased pressure on the cavernous sinus; but this theory of von Graefe has been discounted by the fact that a free anastomosis occurs between the ophthalmic and facial veins; (3) that the intracranial pressure interferes with the return of lymph along the sheath of the optic nerve, caus-

FIG. 322.



Microphotograph of a section of glioma of the pons. × 300.

ing œdema and swelling of the disc. Gowers inclines to the opinion that a combination of causes may be in operation. No doubt simple stasis in the veins would soon be followed by exudation and migration of leucocytes, and all the appearances of inflammation might thereby be produced. In many cases of tumor an ampullary swelling has been observed where the sheath is weak at the entrance to the eyeball.

Regional or focal symptoms are caused either by direct or indirect involvement of structures possessing particular functions. The morbid process may occasion phenomena of an *irritative* character, *e. g.*, a tumor

situated in some part of the Rolandic region may produce unilateral convulsion : or it may be *destructive*, and produce loss of function (paralysis).

Syringomyelia.

This is a *central gliosis* of the spinal cord, causing destruction of the gray matter and *excavation*. The usual seat is around the central canal in the *peri-ependymal* tissue, or behind the canal, in the gray substance of the posterior commissure; thence it invades the anterior and posterior horns. It is usually a neoplastic formation, but according to Charcot it may arise from a central myelitis. The cause of this active growth of embryonic tissue is unknown. The resulting symptoms are *muscular wasting*, and *loss of sensation to heat and cold, and painful impressions*, but preservation of sense of touch. This *sensory dissociation* is peculiarly characteristic of the disease, and goes to prove that Schiff was right in asserting that the gray matter conducts painful sensations, and the posterior columns tactile and muscular sense-impressions. The destruction of the anterior horns produces the muscular wasting, while that of the posterior horns the sensory disturbance, and, *possibly*, the trophic affections that often occur. Of course, the distribution of the motor, sensory, and trophic changes will depend entirely upon the segments of the spinal cord affected. There may be unilateral destruction of the anterior and posterior horns of the same side; and this has been found associated with motor paralysis and sensory disturbance of the same limb or side of the body.

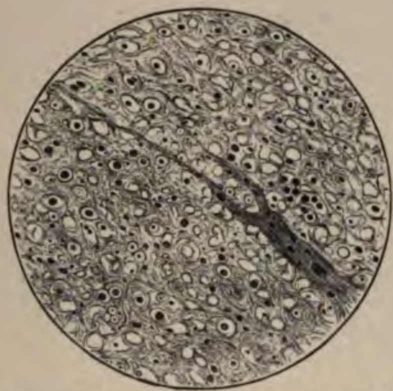
DISSEMINATED CEREBROSPINAL SCLEROSIS.

Insular Sclerosis; Multiple Sclerosis.—This very obscure disease is chhracterized by varying symptoms due to the formation of islands of sclerosis *scattered at random* in the brain, spinal cord, and cranial nerves. It usually attacks healthy young adults of both sexes, and nearly always occurs between puberty and middle life. Many morbid influences have been associated with the disease, *e. g.*, grief, worry, and overwork. As a considerable number of cases have followed an acute specific fever, it has been conjectured that the disease is the result of a toxin.

Morbid Anatomy.—Scattered at *random* through the brain, spinal cord, and nerves are *islets of sclerosis* varying in size from a hemp-seed to a walnut. The naked-eye appearance of these patches varies at different stages of the disease. In the early stage, the morbid process only becomes apparent after the tissue has been hardened in Müller's fluid for a few days, and doubtless this may account for some of those cases which have been confounded with hysteria, owing to the absence of any recognizable lesion on the post-mortem table. In the advanced stage the islets closely resemble gliomata, and present a grayish gelatinous appearance, offering, therefore, a marked contrast to the surrounding white matter, in which they are usually situated. Occasionally the process

extends to the gray matter of the cord and medulla, but very seldom to the cerebral cortex. The term *sclerosis*, however, is a misnomer, as the

FIG. 323.

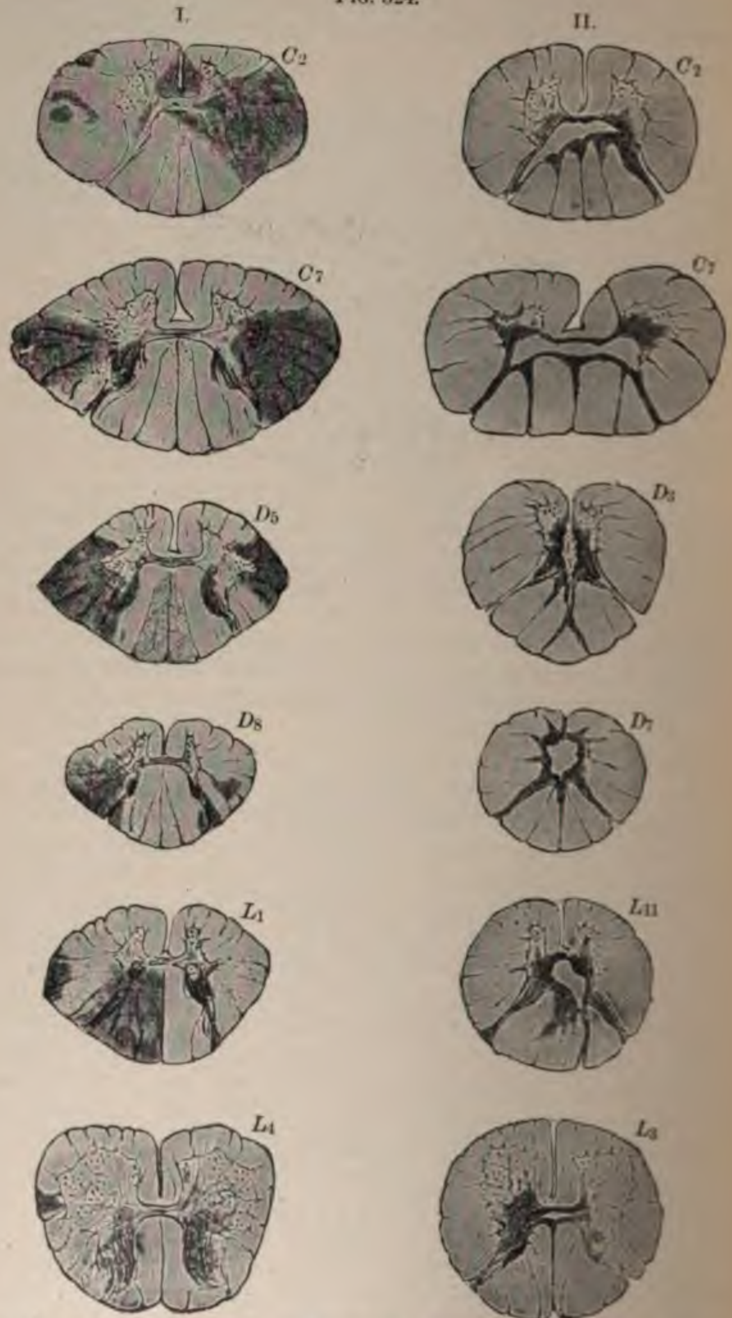


Insular sclerosis. A small portion of the edge of an island of sclerosis. The section shows overgrowth of the neuroglia-tissue at the expense of the white myelin-sheath. The neuroglia stains deeply with carmine. Numbers of black dots are observable in the neuroglia; these are sections of naked axis-cylinder-processes, their myelin-sheath having disappeared. There are some empty spaces in the section, but these are in all probability accidental. × 180.

patches are usually softer than the surrounding tissue. The patches of sclerosis are largest in the centrum ovale, but most abundant and smallest in the spinal cord, although in some cases they may extend in a fusiform manner for a considerable distance.

Histology.—The islets consist of a feltwork of neuroglia, in the meshes of which are a greatly diminished number of nerve-fibres, presenting for the most part morbid appearances especially affecting the myelin-sheath; at the edges of the patch a gradual transition into normal tissue can be observed. Where the process is seen in an early stage there are dilated vessels surrounded with leucocytes; and it may be asked: Is this an inflammatory reaction due to a toxin in the blood, or is it only the reaction to injury of the myelin-sheath of the nerve-fibres? It has long been held that although the medullary sheath is undoubtedly absent, the axis-cylinders persist unchanged throughout the islet; only in this way can we account for the fact that *as a rule systemic degenerations are absent above and below the patches.* But cases do occur in which the axis-cylinders also show well-marked changes and in which they, as well as the sheath, are undoubtedly absent in the sclerosed area. The morbid process appears to begin in the myelin-sheath, which swells up and eventually disappears, its place being occupied by the proliferated neuroglia-tissue. When systemic degeneration occurs it is usually in the crossed pyramidal tracts that it commences. The characteristic rhythmical tremors upon intentional movements have been conjectured to be due to the absence of the myelin-sheath, so that voluntary impulses are not insulated in their passage along the pyramidal tract.

FIG. 324.



A series of sections of the spinal cord. Drawn to scale from cases of (I.) disseminated sclerosis and (II.) syringomyelia. Preparations and drawings made by A. F. Tredgold, Path. Lab. of the London County Asylum.

Syphilitic disease of vessels may produce *single* or *multiple patches* of softening with *secondary sclerosis;* but should these foci of disease be situated in the course of projection-systems secondary degeneration invariably results.

Cerebral Aneurysm.—The causes of aneurysm of the cerebral arteries are the same as of aneurysm elsewhere—viz., *syphilitic arteritis* and *atheroma*, but besides them an even more important apparent factor is infective embolism. The *arteries of the base* are especially prone to be affected, and the size of the aneurysm may vary from a pea to that of a pigeon's egg. The arteries of the left side are more often affected than the right, the carotid system more often than the vertebral. Rupture occurs in rather more than one-half of the cases; the blood most frequently escapes into the membranes at the base of the brain. sometimes into the brain-substance or the ventricle (Fig. 315).

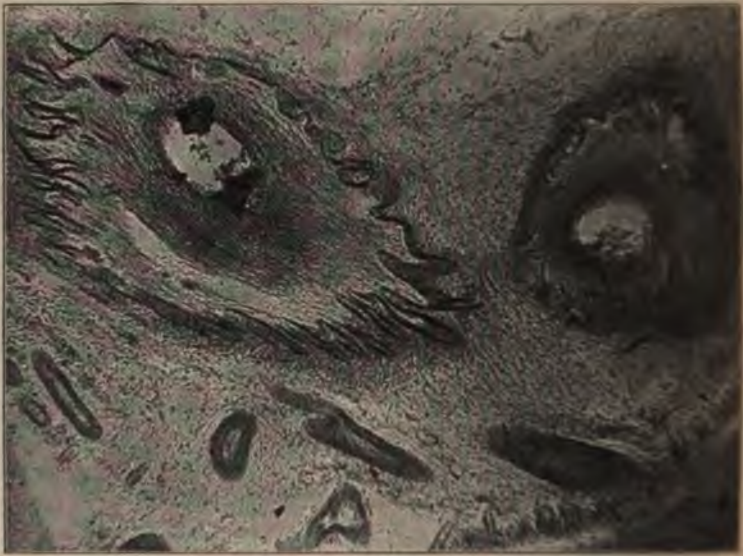
SYPHILITIC DISEASE OF THE CENTRAL NERVOUS SYSTEM.

Syphilis is one of the most important factors in the production of disease of the nervous system. The virus appears to act in two ways: (1) *directly upon the bloodvessels, membranes, and connective tissues* generally, with *secondary destructive changes* in the nervous tissue—a *true specific inflammation;* (2) by a *toxic influence upon the vitality and durability of the neurons* themselves, producing *systemic degenerative changes*, of which *tabes dorsalis* and *general paralysis* are by far the most common and important, although many cases of epilepsy, idiocy, and imbecility are undoubtedly due to the syphilitic poison. These are spoken of frequently as *parasyphilitic* affections (Fournier), and are treated of elsewhere. A frequent result of the disease is an inflammation of the arteries, especially about the base. The specific inflammation causes occlusion, either directly by the *endarteritis* produced, or more often by *secondary thrombosis*. Another very common result of syphilis is a *local or general inflammation* of the *membranes* (*gummatous meningitis*), and the formation of neoplastic deposits (*syphilomata*) on the surface or in the substance of the brain. The meningitis, in severe cases, extends usually to the whole cerebrospinal axis. Each of these cerebral forms of this disease may produce most varied symptoms. Partial or complete occlusion of the vessels may cut off the blood-supply from various portions of the brain, causing *softening* (p. 566) and loss of function (if there is complete occlusion), and disturbance of function, temporary or permanent, according as there is compensatory supply of blood to the part by other vessels or not.

Disease of the arteries may exist alone without any symptoms of *cerebral irritation* or *increased intracranial pressure*—conditions which are met with respectively in the next two varieties. When the membranes are affected by the inflammatory process the vessels are generally also affected, but not necessarily, so that we may have a combination of the effects of cerebral softening and vascular occlusion with cortical

irritation or cranial-nerve paralysis from gummatous meningitis. The *irritation-phenomena* are *pain in the head, worse at night*, sometimes *vomiting* and *convulsions*, and other irritative symptoms, according to the situation of the lesion. Owing to the frequency with which the *base* of the brain is affected, *paralysis of the cranial nerves* is one of the most common results, a partial or complete paralysis of the motor oculi being present in a majority of the cases of cerebral syphilis.

FIG. 325.



Section of gummatous mass in Sylvian fissure, showing almost completely obliterated vessels recognizable as vessels only by the elastic coat. × 70. (*Archives of Neurology*, vol. i.)

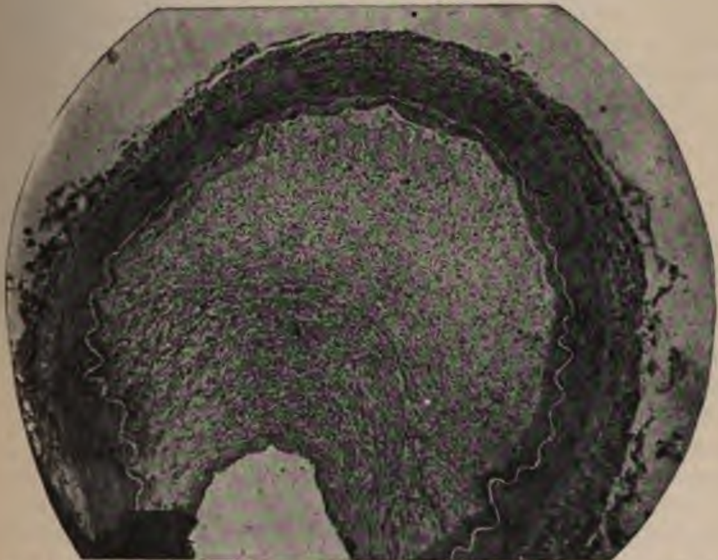
Syphilitic disease of the nervous system may manifest itself at any time from *three months* after infection to *twenty-five* or even more years. It was formerly believed that *syphilitic brain-disease* was essentially a tertiary lesion, but recent carefully recorded statistics show that it *occurs with greatest frequency in the first or second year after infection*, and that the frequency diminishes with each successive year. The determining causes of cerebral syphilis may be blows on the head, exposure to the sun, mental excitement, excesses "in Baccho et Venere," chronic lead-poisoning, and lack or insufficiency of treatment. Brain-disease may also arise in congenital syphilis.

Morbid Anatomy.—The virus of syphilis affects the mesoblastic structures of the brain, and produces a *round-cell infiltration of the membranes*, which may form a superficial colloidal or gelatinous layer, or a deposit in the form of a *node* or *nodule*, or *multiple nodes or nodules*; and this round-cell infiltration may extend from the surface into the substance of the brain along the course of the vessels or into the fissures, filling them with a *gummy mass* (Fig. 325). It is probable, as Wilks pointed out, that gummata do not begin primarily in the

substance of the brain, but are extensions of the neoplastic formation from the surface along the vessels. The membranes thus affected appear thickened locally or generally, the condition depending upon the age of the process. If it is of recent origin, the inflammatory deposit may be soft and gelatinous, or grayish-red, or of a yellowish color; if of some standing, the inflammatory process may have gone on to the formation of scar-tissue. Should the granulation-tissue form a tumor on the surface or in the substance of the brain, a gumma as distinguished from superficial gummatous meningitis occurs. Gummatous tumors may vary in size from a cherry-stone to a pigeon's egg (p. 389).

Gummata are particularly common about the base of the brain, in the neighborhood of the optic chiasma; but they may occur in any part, and may even involve the dura mater and erode the skull, projecting through externally.

FIG. 326.



Transverse section of basilar artery, showing extreme endarteritis syphilitica, causing almost complete occlusion. × 40. (*Archives of Neurology*, vol. i.)

Naked-eye Appearance of the Arteries.—They present little grayish-white nodules on one side usually, so that, when cut across transversely, the nodules present a half-moon appearance. The vessels themselves feel stiff and cartilaginous between the fingers, and will not collapse on pressure. When there is universal arteritis, the vessels, small as well as large, appear opaque, dirty white in color, and their walls thickened, so that they can be cut easily transversely, owing to the resistance they offer. The vessels about the base are particularly liable to this inflammatory change; possibly it is due to the cerebrospinal fluid which exists there in abundance, and which possibly contains the toxin (Fig. 326).

Microscopical Appearances.—Syphilitic arteritis (p. 392) is characterized by proliferation of the subendothelial cells. It generally affects one side of the vessel, but it may affect the whole of the intima. This endarteritis is frequently associated with a peri-arteritis. The inner coat is thickened, owing to a development of spindle-shaped and stellate cells. According to Heubner, these do not undergo caseous degeneration, and he distinguishes it thus from atheroma. There is actually nothing specific in the process, but it is strong presumptive evidence of syphilis when one finds a thickening of the intima which has not undergone caseation. When the arteritis is very acute a new formation of capillaries in the intima may take place.

Thrombosis of the diseased vessel is frequent; subsequent organization of the clot may occur, and eventually the diseased vessel may be converted into a fibrous cord.

Vascular rupture is rare, so also is the formation of aneurism. The important clinical result of endarteritic syphilitica is cerebral softening. The arteries lying in the Sylvian fissure are most frequently diseased; so syphilitic softening of the brain is commoner in the region supplied by the middle cerebral arteries than elsewhere.

CEREBRAL SOFTENING.

Thrombosis and embolism are the most common causes of **cerebral softening.**

Softening from Thrombosis.—This is commonly the result of atheromatous, calcareous, or syphilitic changes in the **cerebral arteries** (p. 462). As a result of the interference with the supply of blood, the cerebral substance undergoes a more or less rapid process of necrosis (p. 31). (Fig. 327.)

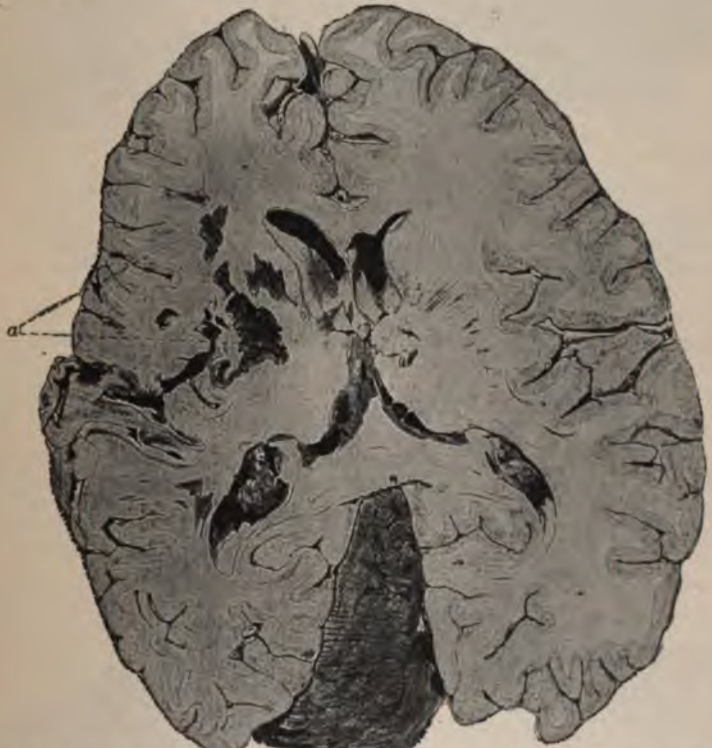
Thrombosis may also occur in the **cerebral sinuses and veins.** Thrombosis of a sinus may be **primary** (marasmic, p. 211), or it may be **secondary** either to (1) disease of some adjacent part, such as of the bone in inflammation of the middle ear; or (2) to extension of a thrombus along a vein—as in the case of the orbit—from an inflamed part to the sinus into which it opens. The result is great distention of all veins opening into the sinus, œdema of the area whence they draw their blood, minute hemorrhages, especially in the vascular cortex, and softening from impaired nutrition (Fig. 329).

Softening from Embolism.—The softening resulting from embolism is, for the most part, entirely dependent upon the obstruction to the circulation caused by the embolus and by the resulting thrombosis. It is rapidly induced, and is often attended by the extravasation of blood in its neighborhood, when it constitutes one form of *acute red softening.* If the interference with the circulation be slight, and there be no extravasation of blood, the softened portions are white in color. The vessel most frequently blocked is the middle cerebral artery; and in the majority of cases it is that of the left side. In almost all cases in

which softening of the cerebral substance results from embolism it is due to arrest of the embolus in one of the vessels *beyond* the circle of Willis, because here the circulation cannot be readily restored by the collateral vessels. Softening, however, does not necessarily follow the blocking of a cortical artery, for communication between these branches is freer than is often supposed (Fig. 328).

It is a matter of considerable importance whether the detached fragment which gives rise to embolism carries infective organisms. If it does, not only is the vessel blocked by the embolus, but an infective inflammation of the arterial wall at the seat of obstruction

FIG. 327.



Cerebral softening of the anterior half of the internal capsule, due to syphilitic thrombosis, from a case diagnosed as epileptic dementia. There was only slight paresis of the right side, but epileptic fits indistinguishable during life from idiopathic epilepsy.

occurs, with softening of the coats and formation of an aneurism, which may subsequently burst; so that a patient suffering from ulcerative endocarditis may die from hemorrhage a short time after embolism of a cerebral artery.

Morbid Anatomy.—The results of embolism and thrombosis are essentially the same—the arterial blood-supply is cut off, and there is

anæmia of the area supplied by the artery. For the first twenty-four hours there is only a slight change in the appearance and consistence of

Fig. 328.

Photograph of brain showing area of softening around the left Sylvian fossa, due to embolism. Case of Dr. Ormerod's. Patient two years before her death had a fit, became paralyzed on the right side; could not speak, but could understand everything; lost sight of the left eye. Eighteen months later had right hemiplegia, word-blindness, motor aphasia, no word-deafness; owing probably to collateral circulation by the anterior cerebral, the upper part of the central convolutions is not destroyed, therefore the hemiplegia was due to softening of the internal capsule. (F. Batten.)

the part, although the neurons may show microscopically well-marked histochemical changes. The affected area has generally a pale appearance; sometimes the capillaries may become distended by a backward flow of blood from the veins, and, giving way, produce small hemorrhages into the perivascular lymphatics. Later on the tissue breaks down and softens, owing to imbibition of cerebrospinal and serous fluids by the dead tissues. When very little blood returns from the

Fig. 329.

Photograph of the cortex cerebri showing red softening due to thrombosis of the great anastomatic vein extending into the longitudinal sinus. The gray matter is deeply stained owing to effused blood, and vascular puncta in places can be seen; in one spot in the white matter it is especially the cortical gray matter which is affected.

veins to the capillaries the area of softening remains *white;* it is red when blood does return from the veins, especially when the walls of the capillaries give way, allowing the red corpuscles to escape.

Since the gray matter is far more vascular than the white, *red softening* is generally seen in the cortex and basal ganglia. *Yellow softening* is merely a later stage of the red, owing to alterations in the blood-pigment.

Microscopically, the softened mass consists of myelin-drops, swollen and degenerated nerve-fibres, altered nerve-cells, and granular corpuscles of Glüge with free fat-granules. These granular corpuscles, which may measure as much as 30 μ in diameter, are leucocytes distended with fatty débris. If the circulation be re-established within a short time, the

FIG. 330.

Cerebral aneurisms. Miliary (right); dissecting (left). × 10. (After Obersteiner.)

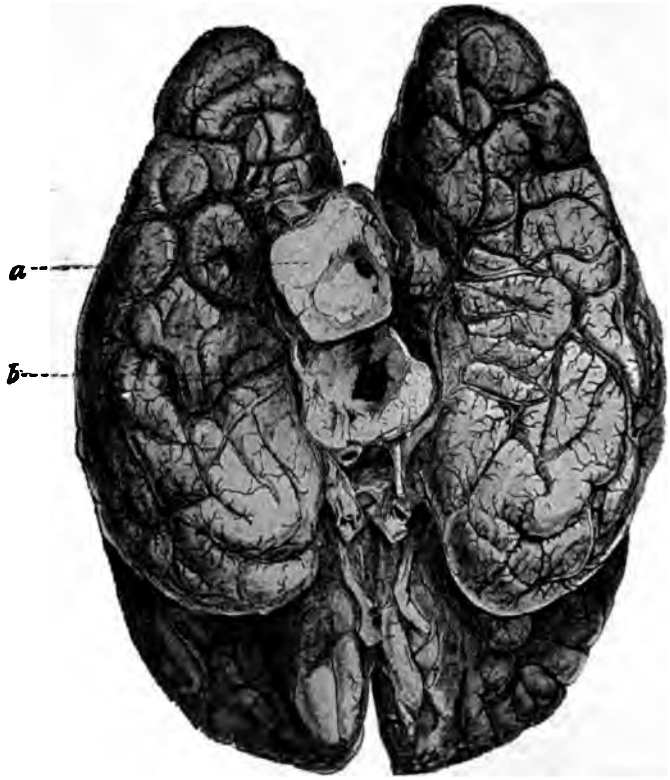
nervous structures do not necessarily die; but regeneration is impossible if necrosis has commenced. Resorption of the dead tissue is gradually brought about, with eventual formation of a *cyst*. If the area is small, a *scar* of fibrous tissue may be the sole indication of the destruction that has taken place. The convolutions of the cortex may sometimes be seen atrophied and sclerotic, especially in senile atheroma; and on tearing off the thickened pia-arachnoid they present little erosions of a rusty yellow color. Sometimes portions of the convolutions, or even a whole lobe, may have entirely disappeared, and the space be occupied by a serous fluid enclosed by the thickened pia-arachnoid membrane.

CEREBRAL HEMORRHAGE.

Cerebral hemorrhage is the most frequent cause of hemiplegia in subjects who have passed forty; and, according to Gowers, it seldom occurs under that age, unless Bright's disease or aneurism exists; the latter produced by infective embolism, and subsequent infective inflammation of the walls of the artery, which may eventually lead to its rupture. The association of granular contracted kidney with apoplexy has long been recognized. Charcot showed that in most cases of hemorrhage minute *miliary* aneurisms, varying in size from $\frac{1}{100}$ in. to

$\frac{1}{25}$ in., existed on the small vessels entering the substance of the brain; they are round or spindle-shaped, and are caused by degenerative changes in the intima, associated with degenerative changes and atrophy of the media. Miliary aneurisms are found with relative frequency in those regions where hemorrhage is most generally met with. There is, however, one artery in particular, the left lenticulostriate artery, which

FIG. 331.



Hemorrhage into pons Varolii, from a case of chronic Bright's disease with miliary aneurisms, one of which had ruptured into the upper part of the pons, giving rise during life to alternate hemiplegia. The pons, lower part (*a*), upper part (*b*), is seen cut transversely to show the hemorrhage.

is especially liable to disease and rupture, and which has therefore been called "the artery of hemorrhage" (Fig. 332). In Bright's disease there is high arterial tension, due to hypertrophy of the left ventricle and increased peripheral resistance (p. 510). Patients suffering from this malady are thus frequently the subjects of cerebral hemorrhage. The small arteries which supply the basal ganglia come off directly at right angles from the large arteries at the base of the brain—they are terminal arteries, and, like all the intracerebral vessels, they are not supported by the substance of the brain, being surrounded by a peri-

vascular lymphatic sheath. Probably these facts explain the frequency of hemorrhage in this situation. Hemorrhage may occur in the cortex,

FIG. 332.

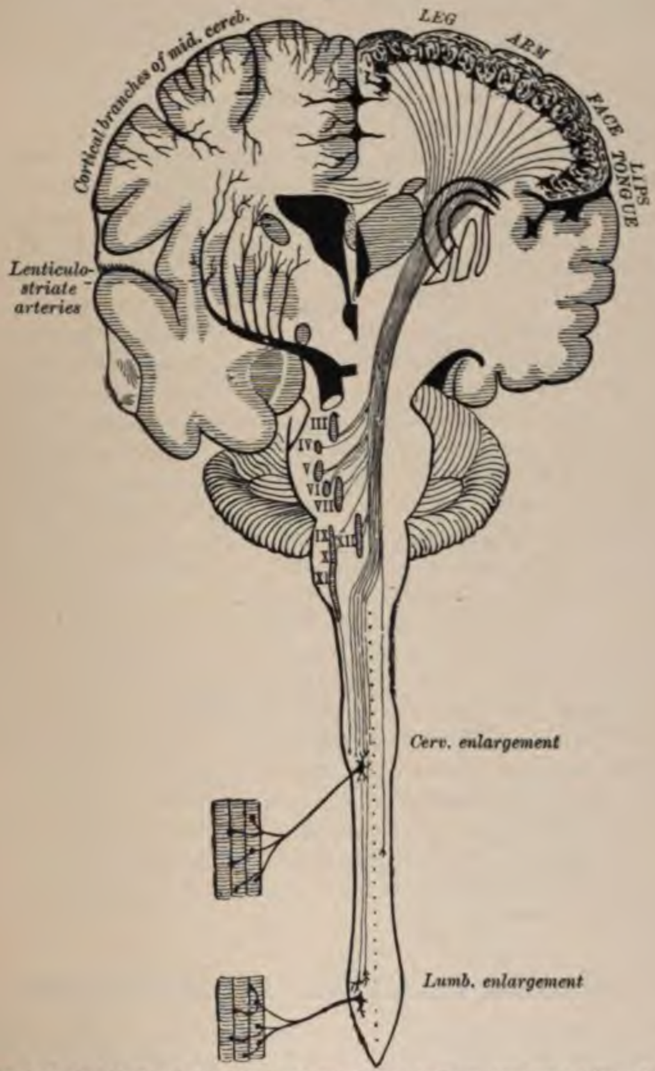


Diagram to show the distribution of the lenticulostriate arteries, coming off from the middle cerebral, rupture of an aneurism on one of which is the frequent cause of apoplexy. It will be seen that as the blood effuses and lacerates the brain-tissue to escape into the lateral ventricle it will destroy successively the axons of the cortical pyramidal neurons as they descend downward to the motor nuclei in the pons, medulla, and cord, giving rise thereby to hemiplegia.

pons, cerebellum, centrum ovale, peduncles, and medulla oblongata (Fig. 331).

Other conditions which predispose to cerebral hemorrhage are plumbism, alcoholism, syphilis, and inherited tendency to arterial disease. It may occur also in tumors. In children *meningeal hemorrhage* may occur, and a frequent cause of birth palsies is rupture of a vessel (usually a vein) during parturition. Subpial, subarachnoid, and subdural hemorrhage is frequently seen in general paralysis and senile dementia. Cerebral or meningeal hemorrhage may occur in various blood-diseases. Primary ventricular hemorrhage occurs in rare instances from rupture of a vessel of the choroid plexus or velum interpositum.

The *effects produced* by hemorrhage depend upon its situation and size; the most frequent seat is the anterior part of the opto-striate mass in the external capsule; but when paralysis occurs, as it usually does, the cause is damage of the pyramidal fibres of the hinder limb of the internal capsule. If the lesion be not severe enough to cause death, various changes occur in the effused blood and damaged nerve-tissues. For the first few days the clot fills the whole cavity, and does not undergo shrinking; then a fatty degeneration takes place, with absorption of the products. In recent cases the effused blood is dark in color, generally clotted, and often mingled with lacerated brain-substance. As changes take place in the blood the color alters first to a chocolate-brown and later to a brownish-yellow. The hemorrhage is usually single, but when small there may be more than one; sometimes evidence of a previous hemorrhage is found in another region, in the form of a cyst with orange-yellow staining of the walls and adjacent brain-substance; or there may be a scar of connective tissue.

In severe cases of hemorrhage causing death, irruption of blood may not only take place into the lateral ventricle of the same side, but also through the foramen of Munro into the opposite lateral ventricle. Occasionally, it may find its way from the third ventricle through the aqueduct of Sylvius into the fourth ventricle; and in rare cases, thence through the foramen of Magendie into the subarachnoid space.

Microscopical examination reveals blood and degenerated nervous tissue, fibres with their myelin-sheath breaking up, granulation corpuscles, degenerated cells, and phagocytes containing products of degeneration. If the hemorrhage is more than a few weeks old, *hæmatoidin*-crystals will be found.

SECONDARY SYSTEMIC DEGENERATIONS.

As a result of destruction of brain-substance, secondary degenerations arise, the most characteristic of which is the secondary descending degeneration arising from destruction of the pyramidal cells of the motor area, or of their fibres in the anterior two-thirds of the posterior half of the internal capsule, such as occurs in cerebral hemorrhage. A similar degeneration may arise as a result of softening due to embolism or thrombosis of the middle cerebral artery or its branches; by meningeal hemorrhage and tumors, or, in fact, by any lesion which causes destruction of the pyramidal cells of the cortex of the central convolutions, or

which cuts off the connection of the nerve-fibres from the cells of which they are the outgrowths (Fig. 332).

As a rule, *cerebral lesions* leading to secondary degenerations are *unilateral*, and *spinal* are *bilateral*. In the former, only one set of pyramidal fibres is degenerated in the spinal cord—viz., those proceeding from one hemisphere by the internal capsule, the middle portion of

FIG. 333.

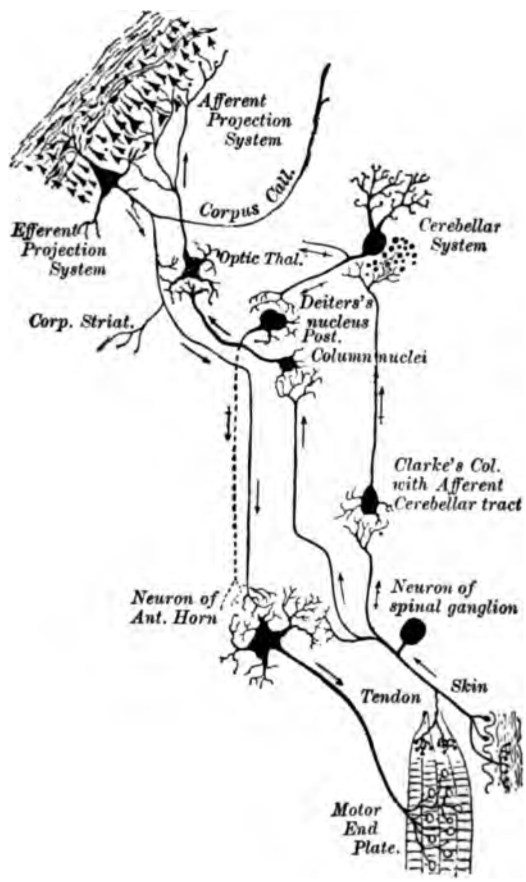


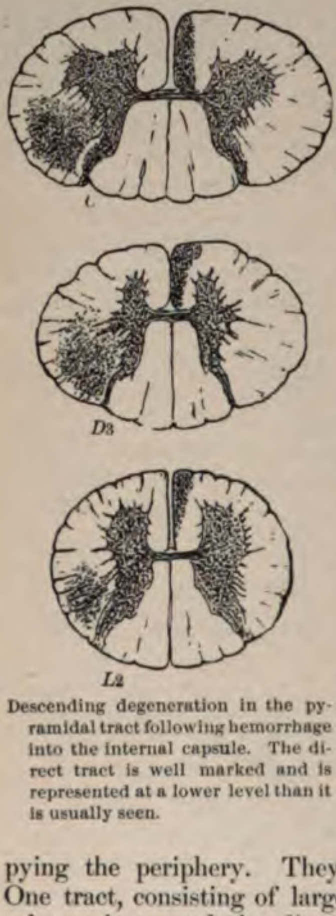
Diagram to illustrate the sensori-motor neurons concerned in conscious voluntary movement.

the crus cerebri, the pons and the medulla, where the greater number decussate in the anterior pyramid to form the crossed pyramidal tract of the opposite side; some (about one-tenth) pass in the direct tract down the cord, decussating at lower levels.

Secondary degenerations arising from lesions of the spinal cord are, in nearly all cases, *bilateral*, and affect not only the *descending* tracts, which have their centres of nutrition in the cortex cerebri, but also the *ascending* tracts, which have their centres of nutrition in the posterior

spinal ganglia and gray matter of the cord. The ascending and descending *ground fibres*, which unite the different segments of the crus, pons, medulla, and cord together in co-ordinate reflex action, degenerate both above and below the lesion for a variable distance; and, besides, there are two tracts in the posterior column, which degenerate downward in transverse lesions of the cord in the dorsal region; they are termed, respectively, the *comma-shaped tract*, and *the median oval area of Flechsig*.

FIG. 334.



Descending degeneration in the pyramidal tract following hemorrhage into the internal capsule. The direct tract is well marked and is represented at a lower level than it is usually seen.

The **ascending degenerations** come under two classes.

(1) *In the Posterior Column.*—Short, medium, and long coursing fibres, having their origin in the central portion of the T-shaped process of the posterior spinal ganglion-cells.

The short fibres form Lissauer's tract, at the base of the posterior horn; the medium fibres enter the postero-external column, and, after a short course, disappear in the gray matter; and the long fibres, after entering the posterior column, are directed backward and toward the median line to form the posterior median (Goll's) column. Secondary degeneration limited to the posterior column indicates a root-lesion, such as from tumor of the cauda equina, or injury of posterior spinal roots (Fig. 333).

(2) *In the Anterolateral Column.*—There are three sets of fibres occupying the periphery. They all arise from cells in the gray matter. One tract, consisting of large fibres derived from the cells of Clarke's column, is termed the *direct or dorsal cerebellar* tract. Another, consisting of two sets of fibres, in all probability arising from cells of the gray matter of the opposite horns, the decussation taking place in the anterior commissure, has several names—viz., Gowers's tract, anterolateral tract, and *ventral cerebellar* tract, because most of the fibres can be traced by a curious course to the middle lobe of the cerebellum. The less numerous fibres enter into the fillet, and probably end at the corpora quadrigemina.

At one time it was thought that all sensory impulses, except those of the muscular sense, decussated immediately on reaching the cord, and this view was held because in most cases of hemilesion of the spinal cord a group of symptoms occurs termed *Brown-Séquard paralysis*, which briefly is *hyperæsthesia and paralysis on the side of the lesion*,

and anæsthesia on the side opposite to it. Latterly Brown-Séquard gave up the theory of immediate decussation of sensory impulses, but maintained justly that as a means of diagnosis the Brown-Séquard phenome-

FIG. 335.

The ascending tracts of degeneration in the cervical enlargement after experimental hemisection of the spinal cord in the mid-dorsal region. The section shows well-marked degeneration of Goll's column, of the direct cerebellar tract and of the anterolateral tracts on the same side as the lesion.

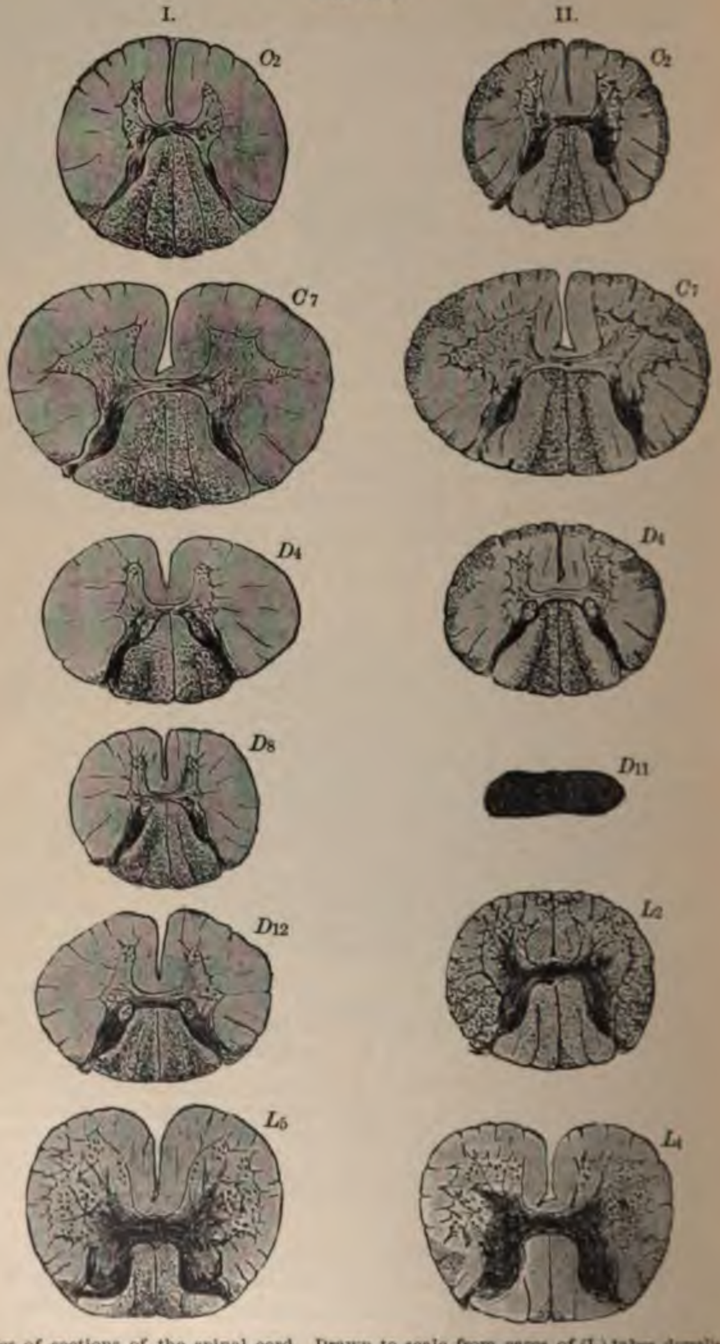
non was most valuable. Hemisection of the spinal cord in monkeys and other animals is followed by paralysis on the side of the lesion, but most recent observers have been unable to find either hyperæsthesia of the same side or anæsthesia of the opposide side (Fig. 335).

FIG. 336.

Photograph of a local gummatous syphilitic meningitis which caused paraplegia. This, however, must be distinguished from the meningomyelitis described by Erb as occurring frequently in the late secondary stage of syphilis which is not of a gummatous nature. Note the thick-walled vessels. The patient was a young woman who died with obscure symptoms which somewhat resembled disseminated sclerosis of the spinal type. Post-mortem it was found that she had multiple syphilitic lesions of the brain and cord. × 10.

The common causes of ascending and descending secondary degenerations of the spinal cord are focal lesions produced by fracture or dislocation of the bones (Fig. 337), pachymeningitis in Pott's disease, meningitis, and tumors, all of which cause a *focal transverse myelitis* (Fig. 336).

FIG. 337.



A series of sections of the spinal cord. Drawn to scale from cases of (I.) tabes dorsalis and (II.) transverse lesion, due to fractured spine. In the former the degeneration is limited to the exogenous tracts of the posterior columns of the spinal cord; in the latter there is ascending degeneration above and descending below the lesion. Preparations and drawings made by A. F. Tredgold, Path. Lab. London County Asylums.

PRIMARY SYSTEMIC DEGENERATIONS.

Primary systemic degenerations may affect either the *afferent* sensory paths or the *efferent* motor paths, and not infrequently the two combined.

I. DEGENERATION OF AFFERENT TRACTS.

Locomotor Ataxy, or Tabes Dorsalis.

Tabes dorsalis is a primary progressive degeneration of the first afferent (sensory) projection systems of neurons, by which peripheral sensations are cut off from various parts of the central nervous system; the commonest and most obvious *anatomical change being degeneration of the posterior spinal roots and the posterior columns of the spinal cord.* The clinical phenomena characteristic of this disease depend upon the systems of neurons which are undergoing degeneration, and on the extent, as well as on the rapidity, of the process.

FIG. 338.

Section of spinal cord about the eighth dorsal segment from a case of locomotor ataxy. There is sclerosis of the postero-external column and atrophy of the fine plexus of nerve-fibrils surrounding the cells of Clarke's column: moreover, a band of sclerosis is seen entering the column instead of the bundle of nerve-fibres. The cells themselves are atrophied and their processes destroyed. The patient had well-marked visceral symptoms—gastric crises, bladder-troubles, and laryngeal crises—in addition to the ordinary ataxic symptoms. × 100 diameters.

Morbid Anatomy.—The pia-arachnoid is thickened over the posterior surface of the cord, which is flattened, and presents a grayish or grayish-red aspect; moreover, the posterior roots are thin, flattened, and atrophied, although the degree of wasting is not necessarily uniform; they also present a gray appearance like the posterior surface of the cord. The cord, cut transversely, shows degeneration limited to the posterior columns, which are considerably shrunken, and of a grayish or grayish-red color, contrasting strongly with the white antero-lateral columns. This degeneration is usually much more obvious and advanced in the lumbo-sacral region; likewise the posterior roots entering in the formation of the cauda equina are, as a rule, atrophied to a greater degree than elsewhere.

The degenerative process is not limited to the afferent spinal projection-systems; various cranial nerves may be degenerated, and especially characteristic is gray atrophy of the optic nerve. The peripheral nerves in many cases exhibit degenerative changes.

The degeneration of the posterior columns of the spinal cord is a *system-degeneration of exogenous*[1] *origin precisely similar in anatomical distribution to that produced by section of the posterior roots*; or, in the case of the lumbosacral region, to that produced by a tumor of the roots of the cauda equina. The fibres of the posterior columns are derived from two sources: (1) Exogenous central projections of the T-shaped processes of the nerve-cells of the posterior spinal ganglia; (2) endogenous projections from cells of the gray matter of the cord: the former are degenerated in tabes, the latter are not; consequently in the lower lumbar region of the cord a small oval area of undegenerated fibres may be seen, even in advanced tabes, occupying the median portion of the posterior column, also a tract of fibres, *the cornu commissural* (Fig. 337). Now, it is impossible to conceive that vascular changes, or impaired nutrition owing to an insufficient supply of blood, could produce in such a small area as the posterior columns of the spinal cord a degeneration of the fibres of exogenous origin, sparing those of endogenous origin and the adjacent fibres of the lateral column. Neither can we believe that the overgrowth of neuroglia-tissue at the expense of the noble elements is anything more than secondary and proportional to the parenchymatous degeneration.

A poison long present in the system can so lower the vitality of the cells of the body as to induce premature decay. In a majority of the cases of tabes there is a history of syphilis; it is probable that this toxin produces the decay of the posterior spinal neurons.

The changes in the cord are usually more or less symmetrical; but the posterior roots are not always equally affected, and the localization and extent of the spinal degeneration will vary accordingly (Fig. 340). As a rule the lumbar roots are first affected; but in rare cases the mischief may begin in the cervical region and leave the lumbosacral intact. Such cases are termed "arm tabes." Visual defects and blindness are not at all uncommon, due to a gray degeneration of the optic nerve. The cranial nerves and their nuclei may also be affected.

Certain tracts in the posterior column degenerate earlier than others. *Charcot's root-zone* is very early the seat of degeneration. The fibres of *Goll's column* are nearly always degenerated. The *zones of Lissauer*—the fine fibres which form a cap to the extremity of the posterior horn, extending a short distance along the external and internal borders of it—degenerate and disappear in the early stages of tabes. Another situation in which early degeneration is said to occur is the terminal arborization of the root-fibres around the cells of Clarke's column. Certain groups of fibres enjoy a particular immunity, and can be seen intact when all the rest of the posterior column is sclerosed: (*a*) the median oval area of Flechsig; (*b*) cornu commissural bundle; (*c*) the posterior internal triangle; but this group does not offer the same resistance as the other two, which are certainly of endogenous origin. The situations of the degenerations are indicated in Figs. 337, 338, and 339.

[1] Nerve-fibres in the spinal cord are said to be *exogenous* when they arise from ganglion-cells situated outside the cord (posterior-root ganglia), *endogenous* when they arise from cells within the cord itself.

Changes are very often present in the cutaneous nerves, and in long-standing cases a portion of the muscular nerves is sclerosed. In cases exhibiting bone disease the nerves supplying the bone have been found degenerated, and, in the neighborhood of a perforating ulcer and similar trophic disturbances, extensive degeneration of the

FIG. 339.

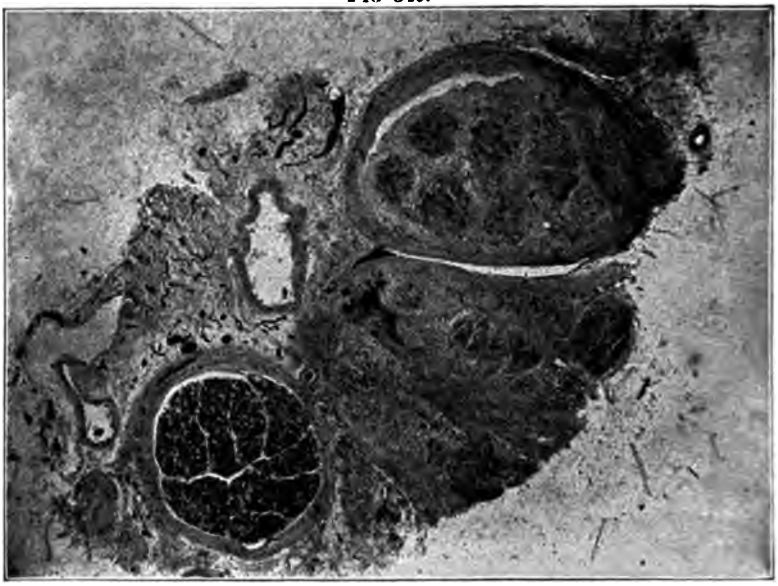
Photomicrograph of section of lumbar enlargement of spinal cord in a case of very advanced tabes, showing extreme sclerosis of the posterior columns. There is complete atrophy of all the fibres except in the median oval area of Flechsig. × 10.

nerves has been observed. The degeneration of the nerves is more marked at the periphery, and the nearer to the cord the point at which the nerve is examined, the fewer degenerated fibres are there found. Slight changes in the cerebral cortex have been described, corresponding to those of general paralysis, but less in degree.

The Nature of the Degeneration.—Microscopical examination of the spinal cord shows the myelin-sheath of the nerve-fibres diminished or destroyed; the axis-cylinder-process may be swollen in one place, attenuated in another, and generally irregular in thickness or completely atrophied; the neuroglia is increased at the expense of the parenchyma, and there are a large number of Deiters's cells visible. Nearly the whole of the posterior columns in the lumbosacral region may be destroyed, leaving only the cornu-commissural and oval areas of endogenous fibres. The vessels are often thickened in the sclerosed area, and not elsewhere; this change is secondary to the degeneration and not causal. The walls of the arteries are often thickened, and there is hyaline degeneration of the media; sometimes the vessels are so much thickened by this degenerative process as to become almost obliterated, especially when the sclerosis is advanced. The pia-arachnoid mem-

brane is also thickened, and often presents the appearances of chronic inflammation. By some authorities this meningeal thickening about the entrance of the posterior roots has been considered to have a causal relation to the atrophy of the fibres in the cord. That tabes is a wide-

FIG. 340.



Photomicrograph of section of anterior and posterior root close to the ganglion, showing the small anterior root with medullated fibres normal, and the sclerosed posterior root much larger in size, but almost denuded of medullated fibres: there is, however, a great overgrowth of fibrous tissue around and between the constituent bundles. × 30.

spread process of degeneration, primary in origin, and not secondary to vascular change or meningitis, is shown by the fact that the vessels of the retina are unaltered, even in advanced gray atrophy.

As a rule, changes in the posterior spinal ganglion-cells are not obvious, but they may be shrunken and pigmented, and exhibit chromolytic changes in advanced cases.

Pathology.—Reference to the diagram (Fig. 333) will help to explain some of the phenomena of tabes, namely, the *diminution of tonus in the muscles*, the *inco-ordination*, the *absence of the knee-jerk*, the *ataxic gait*, *Romberg's symptom*, and the *various disturbances of sensation*.

The afferent system of neurons conveys sensations from the skin, the muscles, tendons, and joints, and these sensations travel by three sets of fibres: (1) *Short*, forming the spinal reflex arc; (2) *Medium* length fibres, which break up into a brushwork around the cells of Clarke's column, the axis-cylinder processes of which form the direct cerebellar tract; (3) *Long fibres*, which form Goll's column and break

up into a terminal arborization around the cells of the nucleus gracilis. There are thus *three nervous circles*—spinal reflex, cerebellar, and cerebral—all of which, in tabes, are more or less interrupted by the degeneration of the fibres in the posterior column. The true motor neuron, which controls the muscle, is situated in the anterior horn. We know that in tabes this is unaffected, therefore the muscle does not waste; nor is there, except in the late stages, any paralysis or loss of strength of voluntary movement, but inco-ordination and a loss of tonus. This is due, like the loss of myotatic irritability and the consequent absence of the knee-jerk, to the break in the reflex spinal arc occasioned by the degeneration of the spinal roots and of those fibres which run forward through the root and the base of the posterior horn, terminating in an arborization around the anterior horn cells. By this degeneration the motor neurons in tabes are deprived of the normal stimuli which serve to maintain the reflex spinal tonus and myotatic irritability.

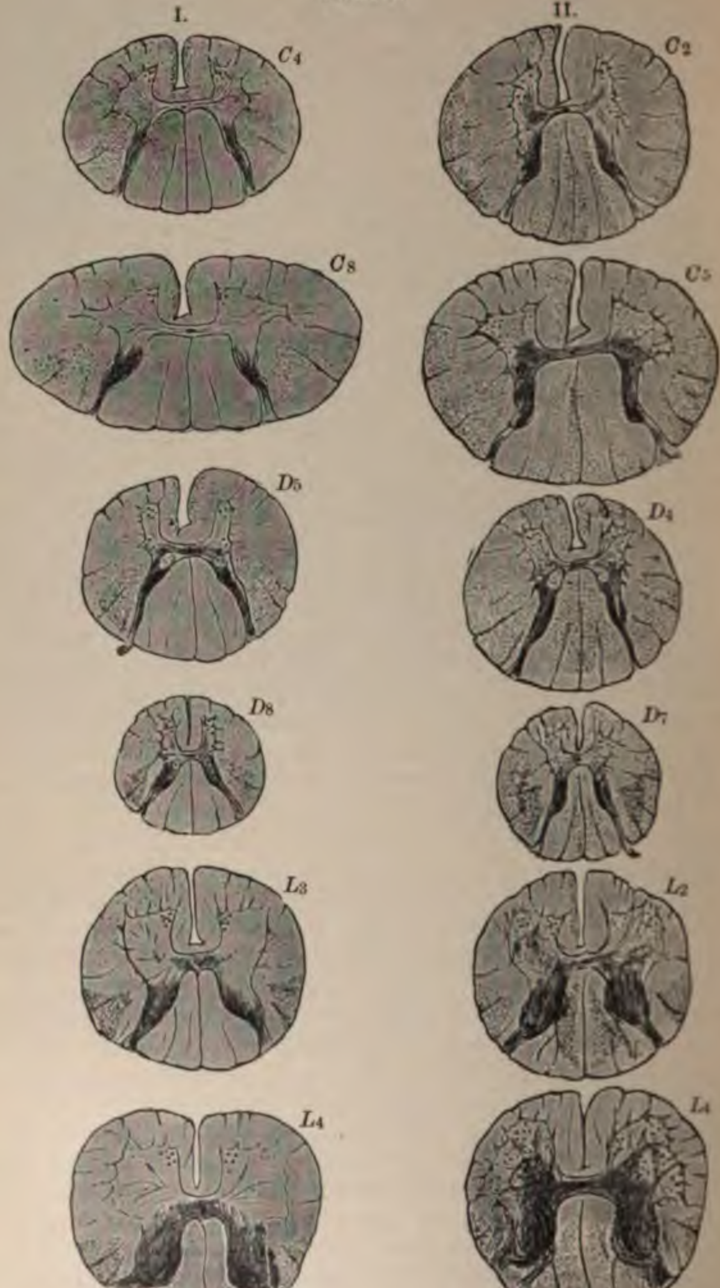
For the maintenance of bodily equilibrium in the erect posture while standing or during the successive changes that occur in the trunk and limbs in progression, a proper adjustment in the contraction of correlative antagonistic muscles is necessary. In standing erect the joints are fixed by the tonic contraction of the antagonistic muscles of the lower limbs. The motor neurons of the anterior horn which preside over the muscles are excited by impulses from the periphery. Unequal and imperfect transmission of sensory impulses will lead to unequal and imperfect excitation of those motor neurons, and to a corresponding unequal and imperfect innervation of the muscles whereby *their normal equable tonic contraction is disturbed and lowered.* Seeing that in tabes there is a progressive degeneration of the afferent spinal neurons, we can easily understand that there will be a progressively lowered and unequal tonus in the muscles.

Again, the degeneration of the fine plexus around the cells of Clarke's column, met with early in the disease, is sufficient to explain the loss of power of balancing the body when the basis of support is narrowed by placing the feet together or standing on one foot, even though there is no paræsthesia of the soles of the feet. Reference to Fig. 333 shows that atrophy of this fine plexus leads to interruption of the sensory afferent impulses to the cerebellum, and puts this organ, which is concerned in maintaining bodily equilibrium in the erect posture, at a great disadvantage. On closing the eyes another guiding sensation is removed and the instability is increased.

The lightning pains may be explained by the degeneration of the root-fibres; but the paroxysmal character is difficult to understand. The partial anæsthesia may be accounted for by the partial degeneration of the roots. Sherrington has shown that at least three roots overlap one another in a skin area, and in order to produce complete loss of sensation in a part all three roots must be divided. If there is pronounced analgesia or anæsthesia, the peripheral nerves are probably affected. With regard to the visceral crises nothing is definitely known.

The Argyll-Robertson pupil is the most constant objective symptom

Fig. 341.



A series of sections of the spinal cord. Drawn to scale from cases of (I.) amyotrophic lateral sclerosis and (II.) combined sclerosis of grave anæmia. In the former there is atrophy of the anterior horn-cells and degeneration of the direct and crossed pyramidal tracts: in the latter there is degeneration of all the long afferent and efferent tracts of the cord. Preparation and drawings made by A. F. Tredgold, Path. Lab. London County Asylums.

of tabes, as it is of general paralysis. No very definite anatomical facts have been brought forward to explain this remarkable phenomenon; but it is asserted that it is due to a break in the junction between the terminal arborization of optic nerve fibres in the corpora quadrigemina and the dendrites of the sphincter iridis nucleus.

Friedreich's Disease.

Friedreich's disease, or *hereditary ataxy*, is a rare disease affecting several members of the same family, the great majority of cases beginning between the fifth and fifteenth years. It is unconnected with hereditary syphilis.

Morbid Anatomy.—There are degenerative atrophy and sclerosis of the posterior columns and posterior roots, but less marked than in tabes; in addition the lateral columns are affected. Frequently there is atrophy of the cells of Clarke's column and sclerosis of the direct cerebellar tracts. Lissauer's tracts, which are always affected in tabes, are in this disease usually unchanged. The affection of the cerebellar tracts is of interest in connection with the typical reeling gait.

Combined Scleroses.

Ataxic paraplegia is a disease in which there is a *combination of the symptoms of lateral sclerosis and of ataxy.* Little or nothing is known as to the cause of the disease.

Morbid Anatomy.—The appearances of degenerative atrophy in the posterior columns of the cord closely resemble those of tabes; but the lateral columns are also affected, especially the crossed pyramidal tracts. The *combined sclerosis* in these regions quite accounts for the combination of symptoms peculiar to this disease. There is usually no history of syphilis, and the Argyll-Robertson pupil is, as a rule, absent.

In *pellagra*, *pernicious anæmia*, and certain grave forms of *anæmia* a degenerative atrophy and sclerosis of the posterior and lateral columns may occur. All the long tracts of the spinal cord may be affected (Fig. 341).

II. DEGENERATION OF EFFERENT TRACTS.

The diseases known as Primary Lateral Sclerosis, Progressive Muscular Atrophy, and Amyotrophic[1] Lateral Sclerosis are probably all due to one and the same pathological process affecting different parts of the motor tract. In the first, the lateral columns of the spinal cord (upper motor segment) are alone affected; in the second, only the cells of the anterior cornua and the peripheral nerves derived from them (lower segment); in the third, both segments of the motor path suffer together.

Primary lateral sclerosis is in all probability due either to a

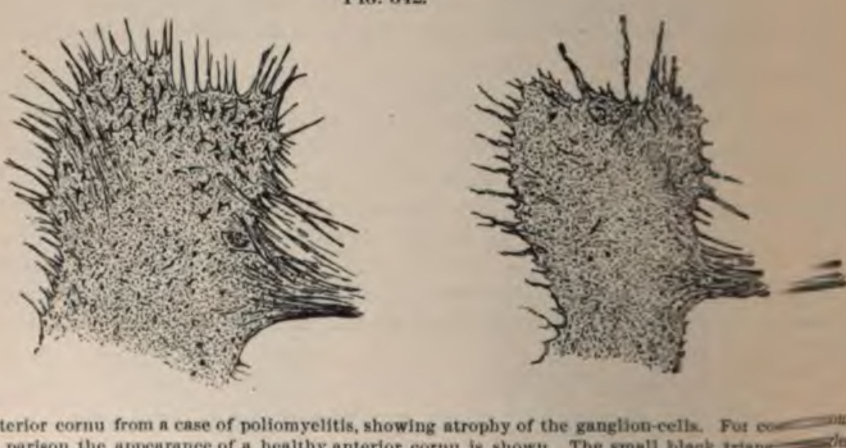
[1] Greek ἀ, not; μῦς, a muscle; τρέφω, I nourish (accompanied by wasting of muscles).

process of softening from vascular occlusion, or to retrogressive nutritional changes in the cells of the motor area of the cortex, owing to which the *pyramidal tracts degenerate.*

In **progressive muscular atrophy** and **amyotrophic lateral sclerosis**, which may be considered together, the lesion of the lower segment is usually most marked. In the former the change begins in the cells of the anterior cornua, usually in the arm-region, and remains confined principally to these cells. The upper segment of the motor tract, however, usually suffers to some extent, the signs of this condition being often masked by the preceding wasting of the muscles. In amyotrophic lateral sclerosis the upper-segment lesion is well marked from an early stage of the disease, rigidity of the legs and increased knee-jerks being often present along with progressive wasting of the muscles of the arms.

In progressive muscular atrophy we find several different types of the disease according to the initial seat of the degenerative process. Sometimes it will begin in the muscles of the shoulder-girdle, sometimes in the small muscles of the hand; the same distinction can be made in the lower limbs. Sometimes the degenerative process will commence in the nuclei of origin of cranial nerves, giving rise to affection of deglutition, phonation, and articulation (*bulbar paralysis*).

FIG. 342.



Anterior cornu from a case of poliomyelitis, showing atrophy of the ganglion-cells. For comparison the appearance of a healthy anterior cornu is shown. The small black triangles represent the cells as they appear under a low magnification.

Morbid Anatomy.—Examination of the spinal cord exhibits degenerative atrophy and sclerosis of the crossed pyramidal tracts and the anterior root-zones (Figs. 341–344). The gray matter of the anterior horns is wasted and greatly deficient in fibres and cells. The large multipolar cells that remain are shrunken, and their processes broken off: in some cases only a little mass of pigment remains. The glia-tissue is increased, and Deiters's cells are very numerous. The regions of the cord affected vary in different types of cases, *e. g.*, when *the*

small muscles of the hand are atrophied the anterior horns are atrophied in the lower cervical and upper dorsal regions. In the amyotrophic form the process commences in the upper pyramidal segment of the

FIG. 343.

Photomicrograph of a section of the cervical spinal cord from a case of amyotrophic lateral sclerosis. Degeneration of the crossed pyramidal and direct tracts and the anterolateral ground-fibres. The direct cerebellar tracts, the anterolateral ascending tracts, and especially the *posterior column*, are unaffected. There was almost complete absence of cells and fine nerve-fibre reticulum in the anterior horns; this is observable by the difference in color as compared with the posterior horns.

motor path. There are, therefore, exaggerated deep reflexes, accompanied or followed by a progressive and characteristic wasting of groups of muscles, owing to degeneration of the anterior horn (Fig.

FIG. 344.

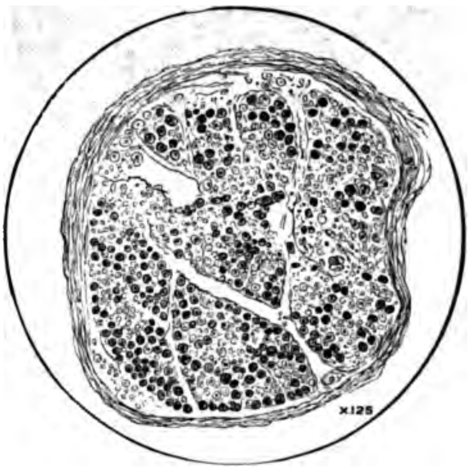
The same as previous figure, except that the section is of the seventh to eighth dorsal segments. The pyramidal tracts are *sclerosed*, and there is considerable degeneration in the intermedio-lateral tract.

342). The peripheral nerve-fibres corresponding to the atrophied spinal motor neurons are atrophied (Fig. 345). The muscles are much

wasted, and in extreme cases can hardly be distinguished from the surrounding fat; but in slight cases they are only pale. Examined microscopically, the fibres are seen to have lost their striation, and many show fatty degeneration.

These cases of amyotrophic lateral sclerosis strongly support the view that there may be a primary retrogressive nutritional change in the neurons, followed by a progressive wasting of the axons, commencing at the terminals, and gradually spreading up the pyramidal tracts; because in

FIG. 345.



Drawing of a section of a fasciculus of the ulnar nerve from the same case, with atrophy of a great number of fibres, stained with osmic acid. For account of the case from which these specimens were taken, *vide Brain*, vol. i. 1895.

some cases the degeneration has been found to extend only as high as the medulla, in others to the pons or crus; while in others, again, the internal capsule and the cortex have been affected. *Bulbar paralysis* is the same disease as progressive muscular atrophy, and is due to a degeneration affecting the motor nuclei of the medulla, particularly a group of cells known as the glosso-labio-laryngeal nucleus. It often forms the final stage of progressive muscular atrophy.

PRIMARY PROGRESSIVE MYOPATHIES.

The etiology of this group of muscular atrophies is still obscure. Heredity plays a prominent part, especially through the maternal side. No definite pathological lesion of the central nervous system has been observed, and the disease is said to be a primary atrophy of the muscle-fibres. *Pseudohypertrophic paralysis* (p. 84), and Erb's *juvenile paralysis* are best known types.

GENERAL PARALYSIS OF THE INSANE.

Etiology.—General paralysis has increased rapidly of late years, and is probably one effect of *syphilization* and *civilization*. It is a disease of large cities and towns, so is syphilis; men are affected much more often than women. The disease has been ascribed to alcohol, but in countries where intemperance is rife yet syphilis absent, general paralysis is unknown—*e. g.*, rural districts of Ireland and Sweden.

Mott has found a history of syphilis and signs of syphilis much more frequently in general paralysis than in other classes of mental disease. Kraft Ebing has shown that eight general paralytics, who exhibited no external signs of syphilis, possessed an immunity to the disease, for they could not be inoculated with the virus.

One of the strongest arguments in favor of the view that syphilis is the factor of all others which causes general paralysis is the existence of a *juvenile form*, occurring in the subjects of congenital syphilis, many cases of which have been recorded by Mott. Other factors, such as worry, anxiety, mental strain and overwork, sexual excesses, alcoholism, blows on the head, sunstroke, and continual mental excitement, act as predisposing or exciting causes. Heredity plays a less important part in this disease than in other forms of insanity.

The etiology of general paralysis and of tabes is very similar; indeed it appears probable that general paralysis and tabes are, pathologically speaking, the same disease, affecting different parts of the nervous system; in the former the brain is affected, in the latter the spinal cord. In each case the process is a primary degeneration of neurons, due to the action of some poison, probably that of syphilis. The inflammatory changes in the membrane and around the vessels, in general paralysis, are in all probability secondary to atrophy of the nervous elements.

Age and Sex.—It affects especially men in the prime of life, in the thirties—the average age of death is 40. It is rare after 50; it may commence (excluding the juvenile form) at 25; but the most common period is between 30 and 40. The disease runs a slower course in women.

Morbid Anatomy.—The dura mater is often found thickened and adherent. Upon opening the dura mater there is obvious atrophy of the brain, especially of the frontal and central convolutions, with *thickening and opacity of the pia-arachnoid;* the sulci present an opalescent, gelatinous appearance, due to the cerebrospinal fluid beneath the thickened membranes. On removing the brain it will be noticed that there is *a great excess of cerebrospinal fluid.* The weight of the organ may be diminished one-third in extreme cases. The lateral ventricles are greatly dilated, owing to the atrophy; the atrophy affects especially the hemispheres, and the *ependyma* of all the ventricles, especially the fourth, is *thickened* and *granular*. If the membranes be stripped from the

hemispheres, it will be observed that, especially in the frontal region, the brain-substance tears away from the membrane, leaving a characteristic worm-eaten appearance (Figs. 346 and 347). The atrophy

FIG. 346.

Photograph of brain of advanced general paralysis. The membranes have been stripped off. The atrophy of the frontal and central convolutions is very evident, as shown by their small size and the depth and width of the sulci.

also affects, but to a less degree, the spinal cord; and there may be obvious naked-eye systemic degeneration, the commonest form of which is similar to that of tabes, although, when examined microscopically, it is generally found that the pyramidal tracts are degenerated. Hemorrhagic pachymeningitis is not uncommon.

Microscopical examination of portions of the brain stained by Nissl's method shows marked thickening of the pia-arachnoid and an overgrowth of the neuroglia-tissue, at the expense of the nervous tissue. The regular layers (forming Meynert's columns) of nerve-cells of the cortex are destroyed, the cells being in all stages of dissolution, from initial swelling with chromatolysis to complete destruction, leaving only the nucleolus recognizable. Some cells are swollen up and no longer retain their pyramidal form; their processes are atrophied and appear broken off; others are almost globular, owing to swelling up of the nucleus, while again others present a shrivelled, atrophied appearance. The motor pyramidal cells do not present the normal Nissl granules, and a single healthy-looking cell in a section of the central convolutions is hard to find. There is a great increase in the *spider cells* of the neuroglia in those situations of the cortex where the atrophy of the nervous elements is most marked, namely, in the frontal and central convolutions and the island of Reil. The vessels are especially visible, owing to dilatation of the perivascular lymphatics and cellular proliferation in the sheath; numbers of leucocytes also are said to be present; the blood contained in the vessels, however, does not usually contain excess of leucocytes. By the Marchi and Marchi-Fal methods two important observations can be made, namely, the existence of a large number of degenerated fibres, in various stages

FIG. 347.

graph of brain of a more recent case of general paralysis; a little time was allowed to apse before stripping the membranes; they were then removed and a worm-eaten eroded rface has been left, due to the adhesions of the thickened membranes.

FIG. 348.

nicrograph of section of cerebral cortex, general paralysis. The columns of Meynert are troyed; the cortical cells are undergoing destructive changes or are destroyed. There is overgrowth of glia-cells, and a vessel is seen surrounded with cells lying in a dilated nphatic sheath. This vessel terminates in the thickened pia-arachnoid membrane. 150.

struction and the *absence of the tangential system of fibres.* Many rities consider the disease to be a primary inflammatory meningo-

encephalitis, with secondary atrophy of the nervous elements. Tabes dorsalis, however, with which the disease is often associated, or by which it may be preceded, was formerly considered to be a primary sclerosis; it is now generally looked upon as a primary degeneration of the afferent system of neurons, with secondary overgrowth of the neuroglia.

The **effect** of the lesions just described is a gradually progressing dementia, owing to atrophy of the association-fibres of the brain. In the early stages tremor of the lips, tongue and hands is generally present; the speech is slurring, and the handwriting unsteady. Delusions are often present. In the final stages of the disease all mental power is lost; consciousness is in abeyance, and voluntary movement is impossible.

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